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(54) **Title:** ANTI-CANCER 2,3-DIHYDRO-1H-PYRROLO[3,2-f]QUINOLINE COMPLEXES OF COBALT AND CHROMIUM

(57) **Abstract:** This invention relates to a class of heterocycles and their metal complexes, and is particularly concerned with the use of these compounds in the preparation of prodrugs or as prodrugs that may be activated under hypoxic conditions by enzymes or by therapeutic ionising radiation, in the treatment of cancer. The invention also relates to the use of these heterocycles and the corresponding metal complexes in the preparation of medicaments and to compositions including the heterocycles or their metal complexes and to methods for preparing these compounds.

Anti-cancer 2,3-dihydro-1H- pyrrolo[3,2-f]quinoline complexes of Cobalt and Chromium.

The present invention relates to novel heterocycles and their metal complexes, and is particularly concerned with the use of these compounds in the preparation of prodrugs or as prodrugs that may be activated under hypoxic conditions by enzymes or by therapeutic ionising radiation, in the treatment of cancer. The present invention also relates to the use of these novel heterocycles and their metal complexes in the preparation of a medicament and to methods for preparing these compounds.

BACKGROUND TO THE INVENTION

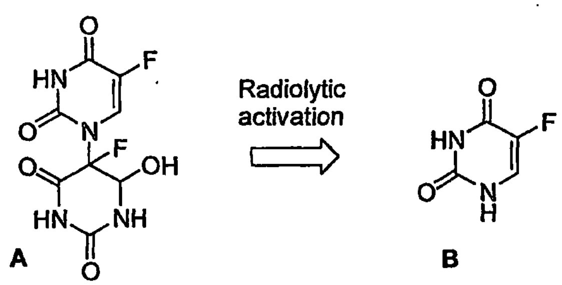
Hypoxic regions occur widely in human tumours, and the cells in these regions are relatively resistant to ionising radiation. This leads to frequent recurrence of tumours after radiotherapy, due to the survival of these radioresistant cells. The use of oxygen-mimetic radiosensitizers has also been widely explored, but with mixed success. The existence of such hypoxic regions, restricted essentially to tumour tissue, has resulted in the development of bioreductive prodrugs (hypoxia-activated prodrugs; HAP) capable of being activated by enzymatic reduction only in these hypoxic regions. The majority of these prodrugs are activated to a transient one-electron intermediate in all cells, but this intermediate is re-oxidised by molecular oxygen in normal tissue, allowing activation to a toxic species to occur only in fully hypoxic cells.

The improved targeting ability of modern radiotherapy to deliver ionizing radiation only to the tumour field has suggested the possibility of using the reducing equivalents from this radiation, rather than cellular enzymes, to activate prodrugs (radiation-activated prodrugs; RAP). The activation of these prodrugs would thus be confined to hypoxic regions within the radiation field, providing a

double level of selectivity. Such a mechanism of activation has other theoretical advantages over HAP [Wilson et al., Anticancer Drug Design, 13: 663-685, 1998]. These include:

- Lack of collateral activation in partially hypoxic normal tissues (outside the radiation field).
- Use of the whole of the hypoxic tumour volume (including necrotic regions with no active reductases or reducing cofactors) to activate the prodrug.
- Avoidance of dependence on possibly varying enzyme levels, and degree of effectiveness as enzyme substrates.

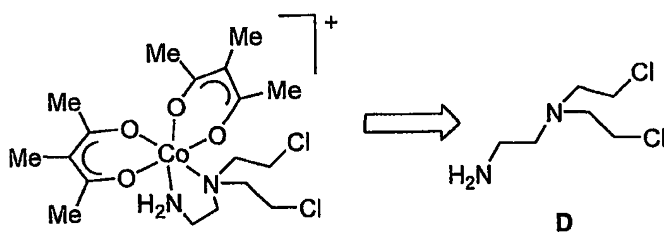
While there have been many reports on HAP [for example reviews by Denny, Lancet Oncol. 2000, 1, 25-29; Stratford and Workman, Anti-Cancer Drug Design 1998, 13, 519-528; Denny et al., Brit. J. Cancer, 1996, Suppl. 27, 32-38], there has been relatively few reports on RAP. An approach to using therapeutic ionizing radiation to activate a prodrug was reported [Nishimoto et al., J. Med. Chem. 1992, 35, 2711; Mori et al; J. Org. Chem., 2000, 65, 4641-4647; Shibamoto et al., Jpn. J. Cancer Res., 2000, 91, 433-438; Shibamoto et al., Int. J. Rad. Oncol. Biol. Phys., 2001, 49, 407-413], employing radiolytic activation of a 5-fluorouracil (5-FU)-based compounds, such as compound A.



However, doses of radiation used during radiotherapy (typically 2 Gy/day) provide a total primary radical yield of only approximately 1.2 μmol/kg. Only about half of this radical yield comprises reducing species capable of activating prodrugs by reduction. Thus the released effector 5-FU; illustrated as compound B above, is not

sufficiently potent to ensure clinically effective concentrations following therapeutic levels of irradiation.

The use of metal complexes of bidentate mustards, such as compound C illustrated below, as RAP has also been reported [Denny et al., PCT NZ96/00085, 19 Aug 1996]. However, the released mustards, such as compound D illustrated below, are also unlikely to be sufficiently potent (IC_{50}s around 1 μM) to ensure clinically effective concentrations following therapeutic levels of irradiation.



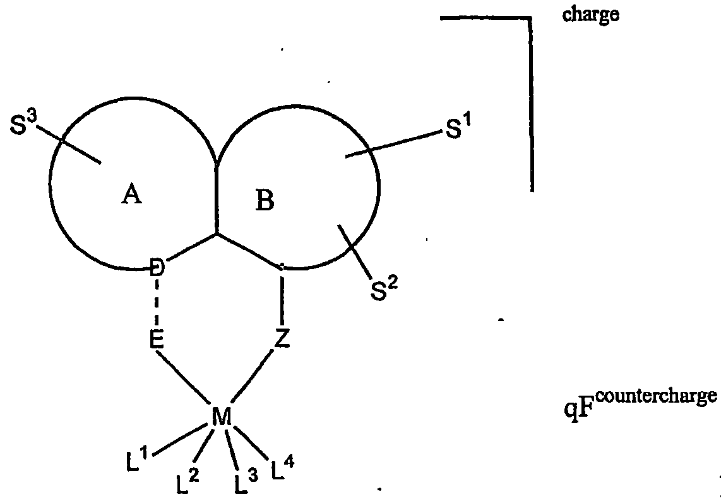
D

C

It is therefore an object of the invention to provide heterocycles and their metal complexes either as prodrugs that are activated under hypoxic conditions by enzymes or other endogenous reducing agents or by therapeutic radiation, or at least to provide the public with a useful choice.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a class of metal complexes represented by Formula I



I

wherein:

A is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

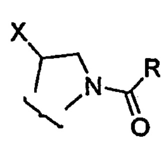
D is selected from C or N;

E is selected from a direct bond, OH or NR^1_2, where each R^1 independently represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, when D represents C; or

M is selected from Co^{III}, Co^{II}, Cr^{III} or Cr^{II};

Z is selected from O, NR^2, where R^2 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups,

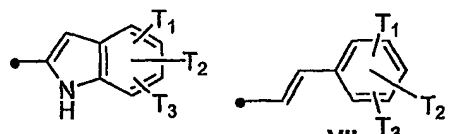
S^1 and S^2 together represent formula V



V

wherein X is selected from a group including CH_2-halogen, CH_2OCO-(C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups), CH_2-phosphate group or $CH_2OSO_2R^3$, where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**

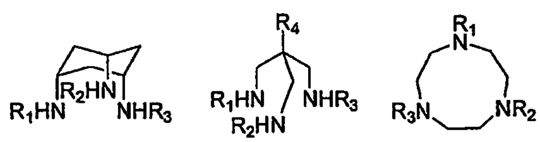


VI VII ,

wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, NR^5_2 or $NHCOR^5$, where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or $O(CH_2)_nNR^6_2$, where each n is independently 1, 2, 3 or 4 and each R^6 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and • represents the point of attachment of R to Formula V defined above, and

S^3 is selected from H, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, CO_2[(C_{1-6}alkyl) wherein said alkyl is optionally substituted with amino, or hydroxy groups]; OR^7, NR^7_2, or $CONHR^7$, where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 5 or 6 membered cyclic system optionally containing one or more hetroeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen groups, and

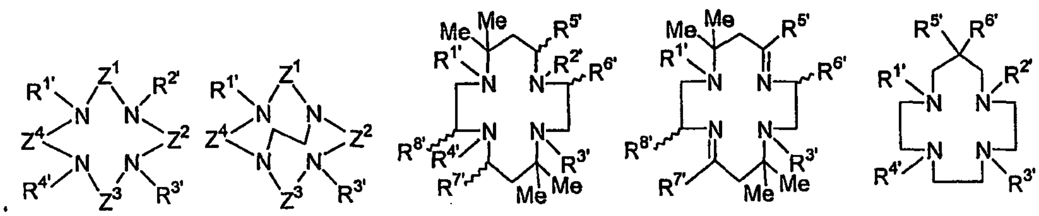
wherein ligands L^1-L^4 are each independently selected in combinations from anionic monodentate ligands, including CN^-, SCN^-, halide, NO_3^-; bidentate ligands including MeCOCHJCOMe (Jacac; deprotonated in the complex), where J = H, Me, Cl, SMe, SO_2Me, $Me_2NCS_2^-$, $S(CH_2)_nSO_3H$, $S(CH_2)_nCO_2H$, $S(CH_2)_nOP(O)(OH)_2$, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$, $CH_2(CH_2)_nOP(O)(OH)_2$, $S(CH_2)_nP(O)(OH)_2$ or $CH_2(CH_2)_nP(O)(OH)_2$, where n is from 1-4;or tridentate ligands **VIIIa-VIIIc** (= respectively TACH, TAME and TACN when R_1-R_3=H),



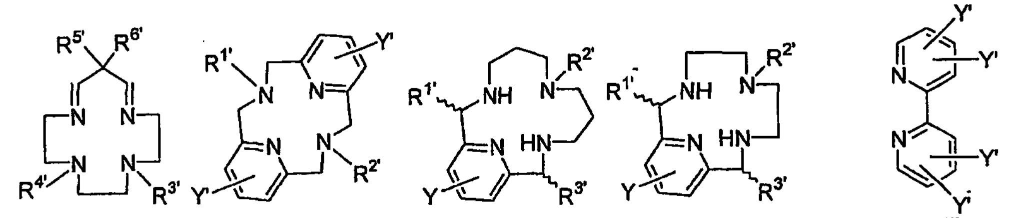
VIIIa VIIIb VIIIc

wherein each R_1-R_4 are independently selected from H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$, $CH_2(CH_2)_nP(O)(OH)_2$, $CH_2(CH_2)_nOP(O)(OH)_2$ or $CH_2(CH_2)_nNR^8{}_2$, where each n is independently 1, 2, 3 or 4 and each R^8 independently represents H, or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or

L^1-L^4 can also be selected from any one of the tetradentate ligands **IX-XVII**, or any two of the bidentate ligands **XVIII**, or any combination of the bidentate ligands **XVIII** together with any of the monodentate ligands L^1-L^4 defined above;



IX X XI XII XIII



XIV XV XVI XVII XVIII

wherein in formulae **IX-XVIII**, $R^{1'}$ to $R^{8'}$ each independently represent H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$, $CH_2(CH_2)_nP(O)(OH)$or $CH_2(CH_2)_nOP(O)(OH)_2$ or $CH_2(CH_2)_nNMe_2$, where each n is independently 1, 2, 3 or 4;

each Z^1-Z^4 is independently selected from $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2OCH_2-$ or $-CH_2N(R^9)CH_2-$; where R^9 represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and

each Y' is independently selected from H, halogen, SO_2Me, $O(C_1$-C_6alkyl), $NR^{10}{}_2$, where each R^{10} is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $Q^1(CH_2)_nQ^2$, wherein Q^1 is selected from –O-, $-CH_2-$, -NH-, -CONH-, $-CO_2-$ or $-SO_2-$, and Q^2 is selected from $-CO_2H$, $-SO_3H$, $-OP(O)(OH)_2$ or $-NR^{11}{}_2$ where each R^{11} is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

wherein the overall charge on the complex is neutral, positive or negative and wherein in the case of a non-neutral complex $F^{countercharge}$ is selected from a range of physiologically acceptable-counterions, including halide$^-$, NO_3^-, NH_4^+ or Na^+; and

wherein q is the required number to neutralise the overall charge on the complex; and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof.

Preferably, the rings A and B of a compound of Formula I as defined above together represent an 8-substituted quinoline system.

In a further aspect the present invention provides a method of providing cancer treatment, which includes the steps of

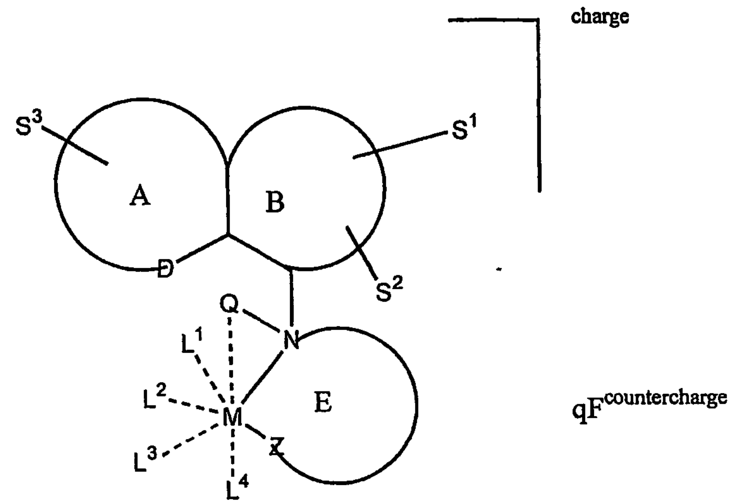
(a) administering to a patient in need of such therapy an effective amount of a compound of Formula I as defined above, and
(b) activating the compound of Formula I under hypoxic conditions via reduction, either enzymatically or by non-enzymatic endogenous reducing agents, or by ionizing radiation,

wherein said activation releases a sufficient amount of an effector from said effective amount of the compound of Formula I.

In a further aspect the present invention further provides a composition comprising as an active agent a compound of Formula I as defined above and a pharmaceutically acceptable excipient, adjuvant or carrier.

In a further aspect the present invention provides the use, in the manufacture of a medicament, of an effective amount of a compound of Formula I for use in treating a subject in need of cancer treatment.

In another aspect, the present invention provides a class of metal complexes represented by Formula Ia



(Ia)

wherein:

A is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

D is selected from C or N;

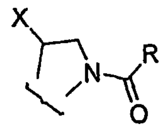
E is selected from a 5 or 6 membered ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

M is selected from Co^{III}, Co^{II}, Cr^{III} or Cr^{II};

Z represents NH_2 or NHMe;

Q represents H, C_{1-6}alkyl or $(CH_2)_2NH_2$, when Q represents $(CH_2)_2NH_2$, Q will become a ligand for M and replace one of ligands L^1-L^4 defined below,

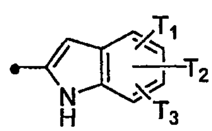
S^1 and S^2 together represent formula V



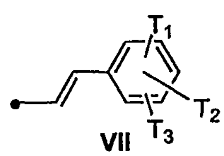
V

wherein X is selected from a group including CH_2-halogen, CH_2OCO-(C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups), CH_2-phosphate group or $CH_2OSO_2R^3$ where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**



VI

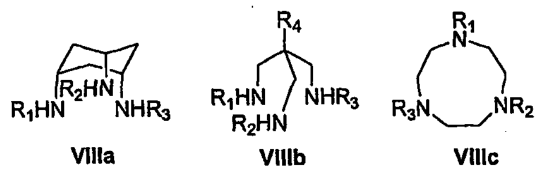


VII ,

wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^2, NR^2_2 where each R^2 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^3_2$, where each n is independently 1, 2, 3 or 4, and each R^3 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and • represents the point of attachment of R to Formula V defined above, and

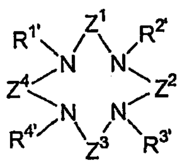
S^3 is selected from H, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, $CO_2(C_{1-6}alkyl)$ wherein said alkyl is optionally substituted with amino, or halogen groups, OR^4, NR^4_2, $CONHR^4$, where each R^4 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more heteroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen groups, and

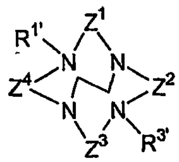
wherein ligands L^1-L^4 are each independently selected in combinations from anionic monodentate ligands, including CN^-, SCN^-, halide, NO_3^-; bidentate ligands including MeCOCHJCOMe (Jacac), where J = H, Me, Cl, SMe, SO_2Me, $S(CH_2)_nSO_3H$, $S(CH_2)_nCO_2H$, $S(CH_2)_nOP(O)(OH)_2$, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nOP(O)(OH)_2$, where each n is independently 1, 2, 3 or 4; or tridentate ligands **VIIIa-VIIIc** (= respectively TACH, TAME and TACN when R_1-R_3=H),



wherein R_1-R_4 are each independently selected from H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nOP(O)(OH)_2$ or $CH_2(CH_2)_nNR^5_2$, where each n is independently 1, 2, 3 or 4 and each R^5 independently represents H, or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or

L^1-L^4 can also be selected from any one of the tetradentate ligands **IX-XVII**, or any two of the bidentate ligands **XVIII**, or any combination of the bidentate ligands **XVIII** together with any of the monodentate ligands L^1-L^4 defined above;


IX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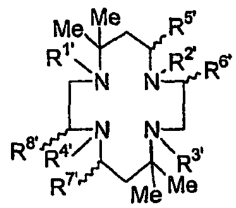
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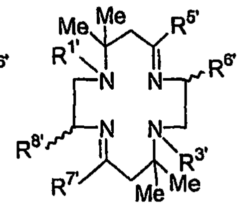
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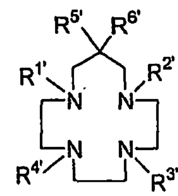
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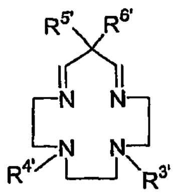
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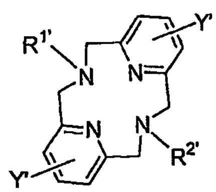
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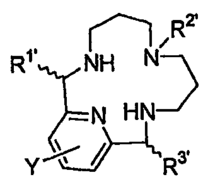
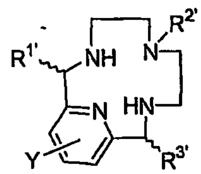
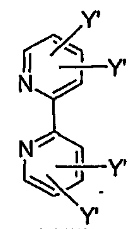

XVI


XVII


XVIII

wherein in formulae **IX-XVIII**, $R^{1'}$ to $R^{8'}$ each independently represent H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nOP(O)(OH)_2$ or $CH_2(CH_2)_nNMe_2$, where each n is independently 1, 2, 3 or 4;
each $Z^{1'}$-$Z^{4'}$ is independently selected from -$(CH_2)_2$-, -$(CH_2)_3$-, -CH_2OCH_2- or -$CH_2N(R^6)CH_2$-; where R^6 represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and
each Y' is independently selected from H, halogen, SO_2Me, O(C_1-C_6alkyl), NR^7_2, where each R^7 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $Q^1(CH_2)_nQ^2$, wherein Q^1 is selected from –O-, -CH_2-, -NH-, -CONH-, -CO_2- or -SO_2-, and Q^2 is selected from -CO_2H, -SO_3H, -$OP(O)(OH)_2$ or –NR^8_2 where each R^8 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and
wherein the overall charge on the complex is neutral, positive or negative and wherein in the case of a non-neutral complex $F^{countercharge}$ is selected from a range of physiologically acceptable-counterions, including halide$^-$, NO_3^-, NH_4^+ or Na^+; and

wherein q is the required number to neutralise the overall charge on the complex, and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof.

Preferably, the rings A and B of a compound of Formula **Ia** as defined above together represent an 8-substituted quinoline system.

In a further aspect the present invention provides a method of providing cancer treatment, which includes the steps of

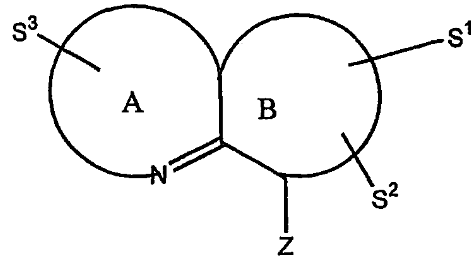
(c) administering to a patient in need of such therapy an effective amount of a compound of Formula Ia as defined above, and
(d) activating the compound of Formula Ia under hypoxic conditions via reduction, either enzymatically or by non-enzymatic endogenous reducing agents or ionizing radiation,

wherein said activation releases a sufficient amount of an effector, from said effective amount of the compound of Formula **Ia**, which is of sufficient potency to kill cancer cells.

In a further aspect the present invention further provides a composition comprising as an active agent a compound of Formula Ia as defined above and a pharmaceutically acceptable excipient, adjuvant or carrier.

In a further aspect the present invention provides the use, in the manufacture of a medicament, of an effective amount of a compound of Formula Ia for use in treating a subject in need of cancer treatment.

In another aspect, the present invention provides a class of heterocycles of Formula **XIX**.



XIX

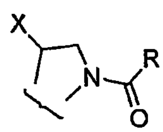
wherein

A is selected from a 5 or 6 membered aromatic ring system optionally containing one or more additional heteroatoms and optionally substituted with one or more $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

Z is selected from OH or NR^1_2, where R^1 separately represent H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;

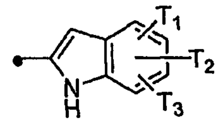
S^1 and S^2 together represent formula **V**



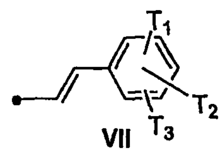
V

wherein X is selected from a group including CH_2-halogen, CH_2OCO-(C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups), CH_2-phosphate group or $CH_2OSO_2R^3$ where R^3 represents H or a $C_{1\text{-}6}$alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a $C_{1\text{-}6}$alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**



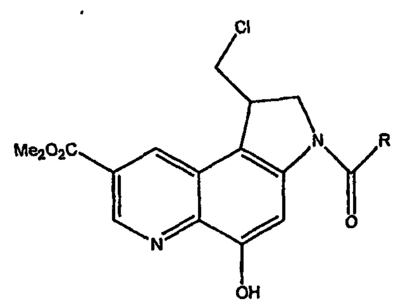
VI



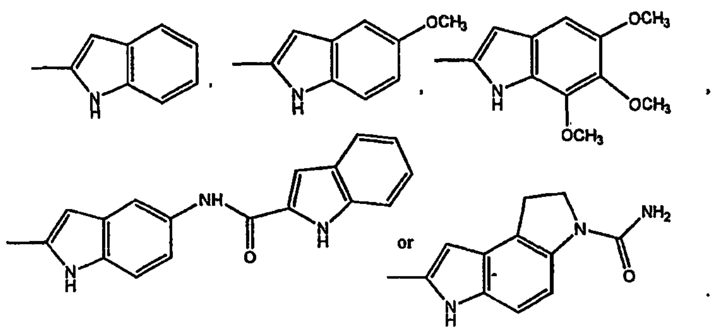
VII ,

wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, $NR^5{}_2$ where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^6{}_2$, where each n is independently 1, 2, 3 or 4 and each R^6 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; • represents the point of attachment to Formula V defined above; S^3 is selected from H, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, CO_2[(C_{1-6}alkyl) wherein said alkyl is optionally substituted with amino, or hydroxy groups], OR^7, $NR^7{}_2$, $CONHR^7$ where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen groups, and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof.

with the proviso that when Z, A, B, X, S^1, S^2 and S^3 together represent

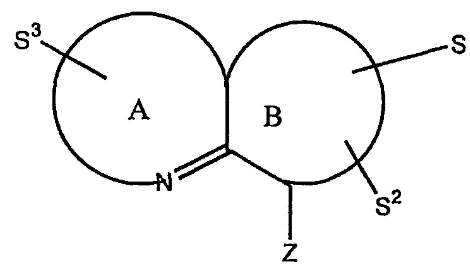


R does not represent one of the following



Preferably, the rings A and B of a compound of Formula **XIX** as defined above together represent an 8-substituted quinoline system.

In a further aspect the present invention provides a method of providing cancer treatment, which includes the step of
administering to a patient in need of such therapy an effective amount of a compound of Formula **XIX**



XIX

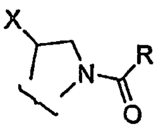
wherein

A is selected from a 5 or 6 membered aromatic ring system optionally containing one or more additional heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

Z is selected from OH or NR^1_2, where R^1 separately represent H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;

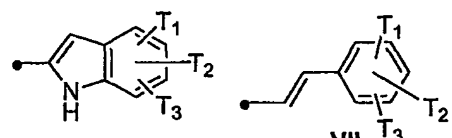
S^1 and S^2 together represent formula V



V

wherein X is selected from a leaving group including CH_2-halogen, CH_2-phosphate group, $CH_2OCO\,R^2$, where R^2 represents C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups; $CH_2OSO_2R^3$ where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydrogen or amino groups; and

R is selected from one of formulae **VI** or **VII**



VI VII ,

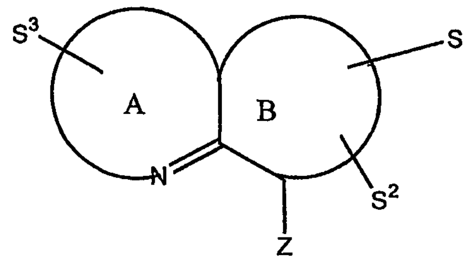
wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, NR^5_2 where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^6_2$, where each n is independently 1, 2, 3 or 4 and each R^6 is independently selected from H or a C_{1-6} alkyl optionally substituted with one or more hydroxy or amino groups;

• represents the point of attachment to Formula V defined above;

S^3 is selected from H, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, $CO_2[(C_1$-$_6$alkyl) wherein said alkyl is optionally substituted with amino or hydroxy groups], OR^7, NR^7_2, $CONHR^7$ where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino,

C_{1-6}alkyl, C_{1-6}alkoxy, and halogen group, and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof.

In a further aspect the present invention provides a composition comprising as an active agent a compound of Formula **XIX**



XIX

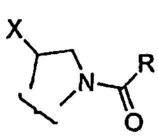
wherein

A is selected from a 5 or 6 membered aromatic ring system optionally containing one or more additional heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

Z is selected from O or NR^1, where R^1 represents H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;

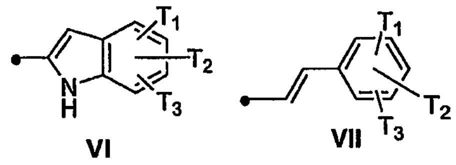
S^1 and S^2 together represent formula **V**



V

wherein X is selected from a leaving group including CH_2-halogen, CH_2-phosphate group, CH_2OCOR^2, where R^2 represents C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups; $CH_2OSO_2R^3$ where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**

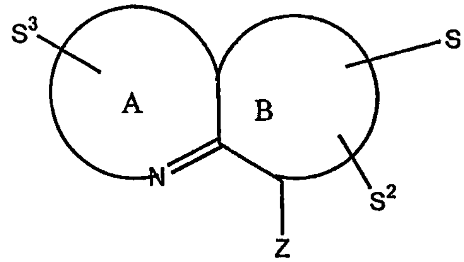


wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, $NR^5{}_2$ where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^6{}_2$, where each n is independently 1, 2, 3 or 4 and each R^6 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups;

• represents the point of attachment to Formula V defined above;

S^3 is selected from H, OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, CO_2[(C_{1-6}alkyl) wherein said alkyl is optionally substituted with amino, or hydroxy groups], OR^7, NR^7, $CONHR^7$ where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen groups; and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof, and a pharmaceutically acceptable excipient, adjuvant or carrier.

In a further aspect the present invention provides the use, in the manufacture of a medicament, of an effective amount of formula **XIX**



XIX

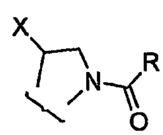
wherein

A is selected from a 5 or 6 membered ring system optionally containing one or more additional heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

Z is selected from OH or $NR^1{}_2$, where each R^1 independently represents H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;

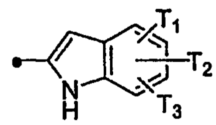
S^1 and S^2 together represent formula **V**.



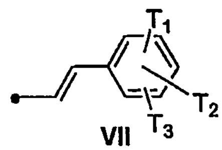
V

wherein X is selected from a leaving group including CH_2-halogen, CH_2-phosphate group, CH_2OCOR^2, where each R^2 independently represents C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups; $CH_2OSO_2R^3$ where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^5$ where R^5 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**



VI



VII

,

wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, NR^5_2 where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^6_2$, where each n is independently 1, 2, 3 or 4, and each R^6 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups;

• represents the point of attachment to Formula **XIX** defined above;

S^3 is selected from H, OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, CO_2[(C_{1-6}alkyl) wherein said alkyl is optionally substituted with amino, or hydroxy groups], OR^7, NR^7, $CONHR^7$ where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen groups, for use in treating a subject in need of cancer treatment, and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof.

It is to be recognised that the compounds of the invention defined above can exist in different enantiomeric and/or diastereomeric forms. In such cases it is to be understood that formulae **I**, **Ia** and **XIX** can represent any possible enantiomeric or diastereomeric form, or any mixtures of such forms, and also any physiologically functional salt derivatives thereof.

In a final aspect, the present invention provides methods of preparing compounds of the general formulae **I**, **Ia** and **XIX** defined above. Such methods are described below.

It is to be understood that the terms C_{1-6} alkyl and C_{1-6} alkoxy as used throughout the specification are to be taken as including both the straight and branched forms of such groups.

DESCRIPTION OF THE DRAWINGS

While the invention is broadly defined above, it will be appreciated by those skilled in the art that further aspects of the invention will become apparent with reference to the following Figure and Examples, given by way of example only, wherein

Figure 1 shows graphically the release of a cytotoxic effector **18a** (SN 26800) from a compound of Formula I **M1** (SN 27892) when irradiated in formate buffer, pH 7.0 under hypoxic conditions.

Figure 2 shows graphically the hypoxic selectivity of metal complex **M1** in HT29 cultures.

DETAILED DESCRIPTION OF THE INVENTION

As defined above, this invention provides novel heterocycles and their metal complexes, and is particularly concerned with the use of these compounds, as pro drugs activated under hypoxic conditions by enzymes or by therapeutic ionising radiation, in the treatment of cancer.

In order to ensure that the complexes (pro drugs) of Formula **I** and **Ia** and the heterocycles (cytotoxins or effectors) of Formula **XIX** of the present invention are clinically effective, the complexes and heterocycles would preferably have the following properties

- high chemical stability of the +III metal oxidation states

- minimal toxicity as a prodrug prior to reductive activation by enzymes or radiation
- upon activation the prodrug releases a potent cytotoxic or effector unit

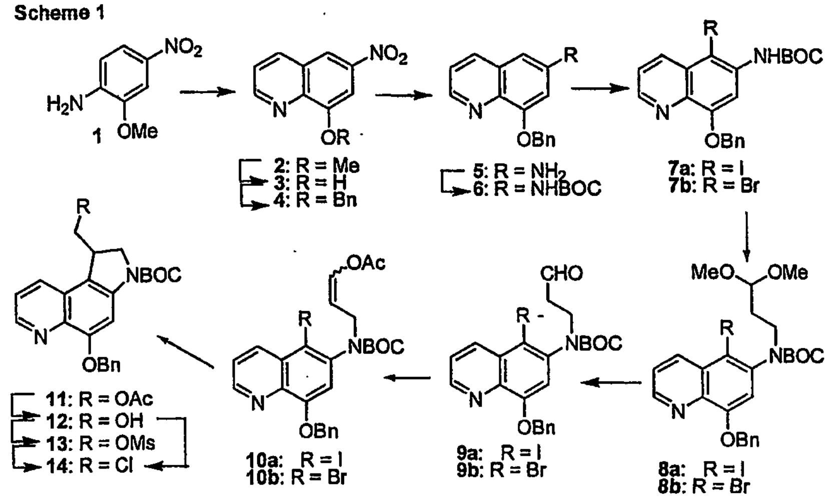
Examples of pro drug complexes or heterocyclic compounds that fulfil these general criteria include the compounds of Formula **I**, **Ia** or **XIX** as defined above. These compounds can be prepared by the following schemes and processes as described below by way of example only.

Preparation Example 1

A: Synthesis of 5-hydroxy-2,3-dihydropyrrolo[3,2-f]quinolines

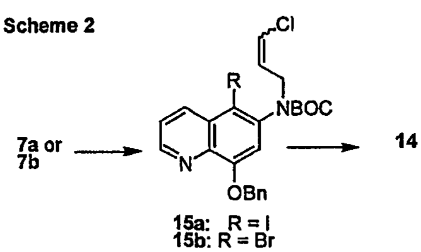
In general, 5-hydroxy-2,3-dihydropyrrolo[3,2-f]quinolines of formula (**XIX**; Z=O) can be made from the precursor **14**, that in turn can be prepared by the method outlined in Scheme 1. Conversion of the known [Curd et al., J. Chem. Soc., 1947, 69, 1613] **1** by the Skraup reaction gives **2** in 80% yield, using an improved procedure [Battersby et al., J. Chem. Soc. Perkin Trans. I, 1979, 2250]. Conversion of methyl to benzyl (**2**→**3**→**4**) (to allow more ready removal at the end of the synthesis), followed by reduction of **4** with Fe/AcOH gives **5**. This can beBOC-protected to give **6**, which can be iodinated with NIS/MeCN to give **7a** or brominated (NBS/MeCN) to give **7b**. Alkylation of **7a/7b** with 3-bromo-1,1-dimethoxypropane gives **8a/8b**, which can be deprotected (TsOH) to **9a/9b**, then converted to the vinyl acetates **10a/10b** (Ac_2O, DMAP, THF, reflux). These undergo radical cyclization (Bu_3SnH/AIBN) to give **11**, which can be deprotected (Cs_2CO_3) to give **12**. This can be converted either directly (Ph_3P, CCl_4) or *via* mesylate **13** (MsCl, Et_3N; then LiCl, DMF) to the desired racemic pyrroloquinoline **14**.

Scheme 1



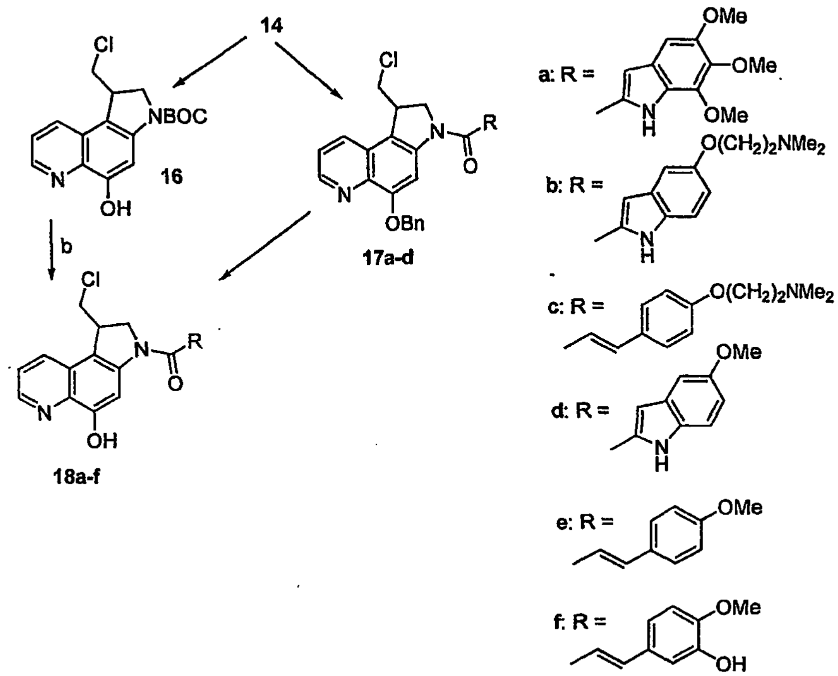
An alternative and shorter route from **7a/7b** to **14** is shown in Scheme 2. N-Alkylation of **7a/7b** with 1,3-dichloropropene, and radical cyclization of the resulting vinyl chlorides **15a/15b** gives **14** in high yield.

Scheme 2



The benzyl group of **14** can be removed by hydrogenolysis (Scheme 3), and the resulting phenol **16** can be N-deprotected and coupled with appropriate side chains R (formula **XIX**). An alternative route is by N-deprotection/coupling, followed by removal of the benzyl group (**14**→**17**→**18**), either by hydrogenolysis or by acid treatment.

Scheme 3



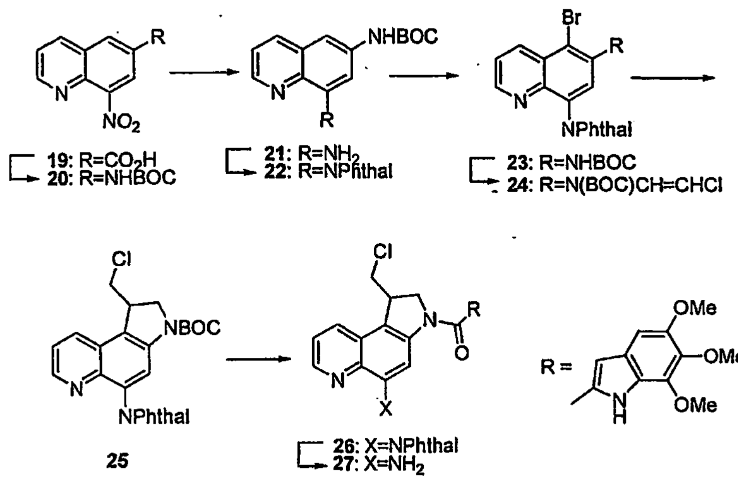
Preparation Example 2

Synthesis of 5-amino-2,3-dihydropyrrolo[3,2-f]quinolines

In general, 5-amino-2,3-dihydropyrrolo[3,2-f]quinolines (**XIX**, Z represents NH_2) can be prepared from the precursor **25**, which can be synthesized by the method outlined in Scheme 4. The quinoline acid **19** [Jung et al., Eur. Pat. Appln. EP 581500 (1994); Chem Abstr, 1994, 122, 205125], prepared by a Skraup reaction on ethyl 4-amino-3-nitrobenzoate, is converted with DPPA/t-BuOH/Et_3N to the quinoline **20**. Nitro group reduction gives amine **21**, which is converted to the phthaloyl derivative **22**, and then brominated (NBS/MeCN) to give **23**. N-Alkylation of this with 1,3-dichloropropene, followed by radical cyclisation of the resulting chloro intermediate **24** with Bu_3SnH/AIBN, gives the tricyclic pyrroloquinolinone **25**. As shown in Scheme 4, NBOC deprotection of **25** followed by EDCI coupling with acids gives the compounds of formula **26** (illustrated for the example where R=5,6,7-trimethoxyindol-2-yl). Finally, deblocking of compound **26** by hydrazinolysis gives compounds of formula **XIX**,

where Z represents NH_2 (illustrated for the example where R=5,6,7-trimethoxyindol-2-yl; **27**).

Scheme 4

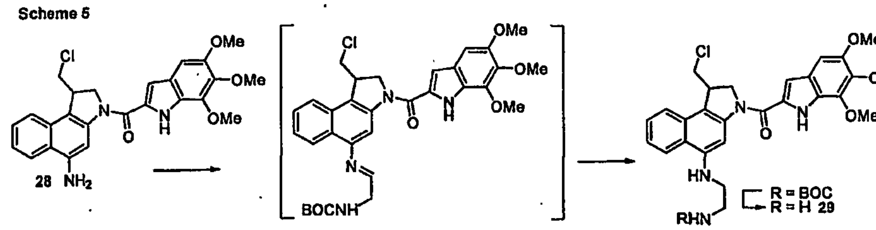


Preparation Example 3

Synthesis of 5-(2-aminoethylamino)benz[e]indoles

These can be prepared from the appropriate 5-amino compounds by condensation with the BOC-protected aminoacetaldehye, followed by reduction with sodium cyanoborohydride or other suitable reductants, and deprotection of the BOC group. Scheme 5 shows the synthesis of the representative compound **29** from the known [Atwell et al., J. Org. Chem. 1998, 63, 9414-9420] 5-amino compound **28**. It will be appreciated that this synthesis can also be applied to the preparation of the analogous derivative from the 5-aminoaza compound **27**.

Scheme 5

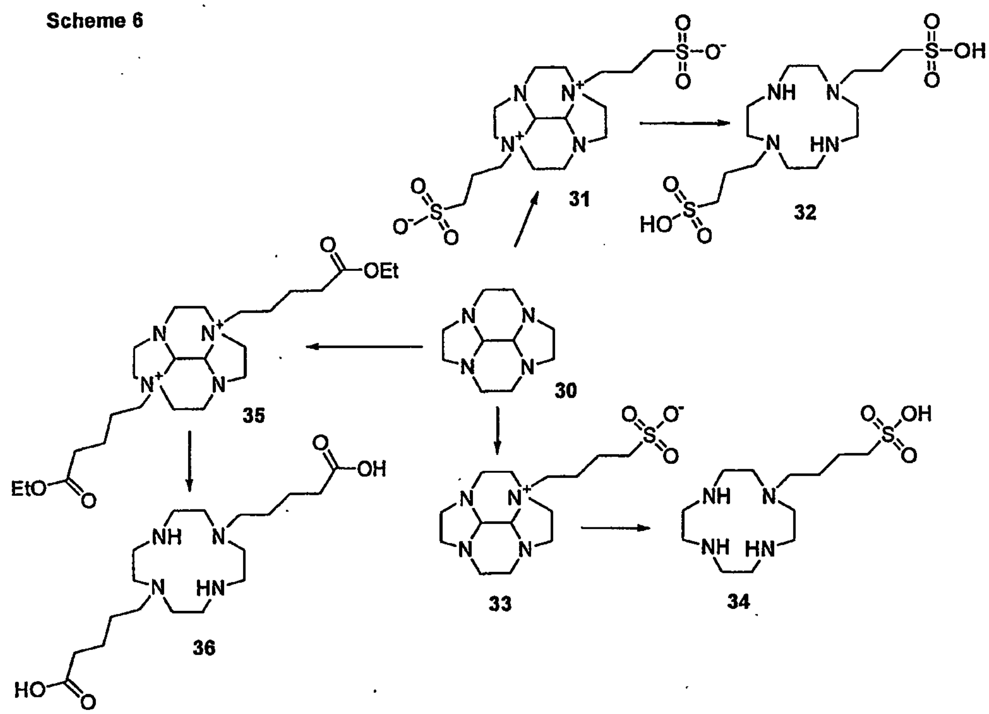


Preparation Example 4

Synthesis of ancillary ligands

As an example of the synthesis of new ancillary cyclen-type tetradentate ligands, reaction of perhydro-3,6,9,12-tetraazacyclopenteno[1,3-*f*,*g*]acenaphthylene (**30**) [Weismān et al., Tetrahedron Lett., 21, 1980, 335] with 1,3-propanesultone gives the bis-quaternary salt (**31**), which is treated with hydrazine monohydrate to give the bis(propanesulfonic acid) (**32**) (Scheme 6). It will be appreciated that similar reaction of **30** with other alkylating reagents will give other analogues, such as those represented as compounds **33** to **36** in Scheme 6.

Scheme 6

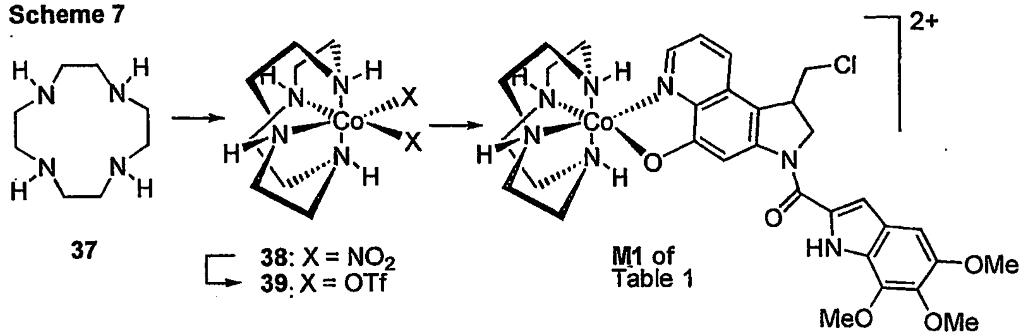


Preparation Example 5

Synthesis of metal complexes

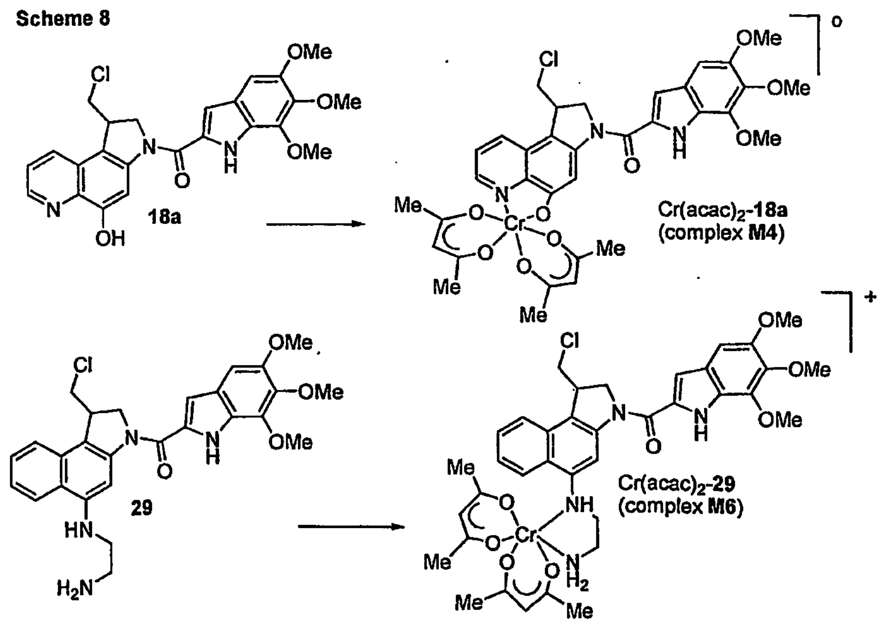
As an example of the synthesis of metal complexes of Formula **I** defined above, using a tetradentate ancillary ligand, reaction of complex **39** bearing labile triflate ligands with **18a** gives the Co^{III} complex **M1**, as illustrated in Scheme 7.

Scheme 7



As an example of the synthesis of metal complexes of Formula **Ia** defined above, using bidentate ancillary ligands, reaction of **18a** with $[Cr(acac)_2(H_2O)_2]ClO_4]\cdot 2H_2O$ in dry CH_3CN gives the desired $Cr(acac)_2$-**18a** complex **M4**. This reaction pathway is represented in Scheme 8. Similar reaction of **29** gives the corresponding $Cr(acac)_2$-**29** complex **M6**.

Scheme 8

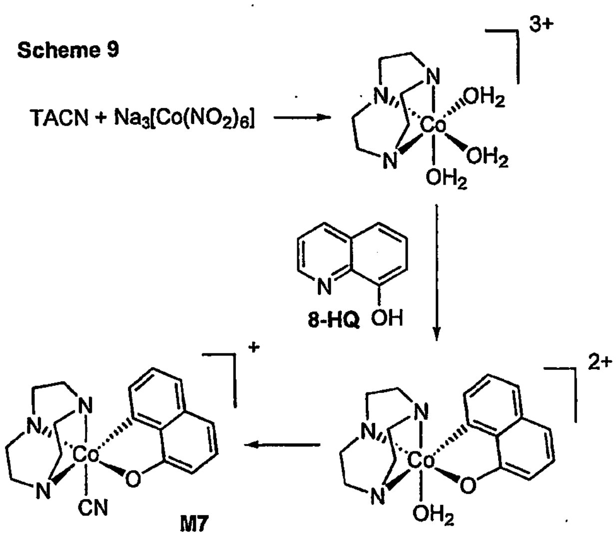


Cr^{III} complexes with other tetradentate macrocycles may be prepared by a similar synthetic route to that employed in the example above using Co^{III}, in that the key

intermediate for both is a reactive bis[triflato] complex (or a solvent species in solution). The use of nitro complexes as precursors to triflato complexes is unlikely for Cr^{III}, as nitro is a poor ligand on Cr^{III}. Instead, chloro complexes serve the purpose well. In the strongly acidic triflic acid, protonation of coordinated Cl^- is significant and leads to labilization and ligand loss, made irreversible by removal of the gaseous HCl co-product.

As an example of metal complexes with tridentate ligands, reaction of the triamine TACN with $Na_3[Co(NO_2)_6]$ gives the complex $[Co(TACN)(H_2O)_3].(OTf)_3$ (Scheme 9). Reaction of this with the model quinoline 8-hydroxyquinline (8-HQ) gives complex **M7**.

Scheme 9



EXAMPLES OF THE INVENTION

The following examples of metal complexes **M1-M9** in Table 1 are representative of the complexes of the invention and can be prepared by the detailed processes of the invention described after the table.

Table 1. Structures and physical properties of metal complexes

No	Metal	toxic ligand	Ancillary ligands	Analyses
M1	Co^{III}	**18a**	Cyclen (**IX**; Z^1-Z^4 = -$(CH_2)_2$-, $R^{1'}$-$R^{4'}$ = H)	$C_{32}H_{41}N_7{}^{35}ClCoO_5$ $[M\text{-}2ClO_4\text{-}H]^+$ Calc: 697.21897 Fd: 697.21327
M2	Co^{III}	**18c**	Cyclen (**IX**; Z^1-Z^4 = -$(CH_2)_2$-, $R^{1'}$-$R^{4'}$ = H)	$C_{33}H_{45}{}^{35}ClCoN_7O_3$ $[M\text{-}2OTf]^+$ Calc: 681.26044. Fd: 681.26064
M3	Co^{III}	**18b**	Cyclen (**IX**; Z^1-Z^4 = -$(CH_2)_2$-, $R^{1'}$-$R^{4'}$ = H)	$C_{33}H_{44}{}^{35}ClCoN_8O_3$ $[M\text{-}2OTf]^+$ Calc: 694.25569. Fd: 694.25305
M4	Cr^{III}	**18a**	$(Acac)_2$ $(MeCOCH_2COMe)_2$	$C_{34}H_{36}N_3{}^{35}ClCrO_9$ $[M+H]^+$ Calc: 717.15452 Fd: 717.15198
M5	Co^{III}	**18a**	$(Me_2dithiocarbamato)_2$ $(Me_2NSC_2)_2$	
M6	Cr^{III}	**29**	$(Acac)_2$ $(MeCOCH_2COMe)_2$	$C_{37}H_{43}N_4{}^{35}ClCrO_8$ $[M\text{-}ClO_4]^+$ Calc: 758.21745 Fd: 758.21834
M7	Co^{III}	**8-HQ**	TACN (**VIIIc**: R^1-R^3 = H))	

<u>Example A. Preparation of 1-(chloromethyl)-5-hydroxy-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (**18a**) and analogues **18b-18f** by the methods of Schemes 1-3.</u>

8-Hydroxy-6-nitroquinoline hydrobromide (3). A solution of 8-methoxy-6-nitroquinoline (**2**) [prepared from 2-methoxy-4-nitroaniline **1** by the method of Battersby et al., J. Chem., Soc. Perkin Trans. 1, 1979, 2550] (50.0 g, 0.245 mol) in 48% aqueous HBr (0.205 L, 1.22 mol) was stirred at reflux for 65 h. The mixture was cooled in ice and the precipitate was removed by filtration and dried in a desiccator to give **3** as the hydrobromide salt (58.0 g, 87%): subl. 140 °C, mp >230 °C; ^{1}H NMR (DMSO) δ 10.69 (br s, 2 H), 9.20 (dd, *J* = 4.9, 1.5 Hz, 1 H),

9.11 (dd, $J = 8.5, 1.5$ Hz, 1 H), 8.64 (d, $J = 2.4$ Hz, 1 H), 8.05 (dd, $J = 8.5, 4.9$ Hz, 1 H), 7.90 (d, $J = 2.4$ Hz, 1 H); ^{13}C NMR (DMSO) δ 152.0, 149.4, 146.4, 144.3, 135.4, 128.3, 124.1, 114.5, 106.5. Anal. Calcd for $C_9H_6N_2O_3$.HBr: C, 40.01; H, 2.61; N, 10.37. Found: C, 40.44; H, 2.17; N, 10.83.

8-Benzyloxy-6-nitroquinoline (4). A mixture of 3 (58.0 g, 0.214 mol), DMF (400 mL), K_2CO_3 (103.5 g, 0.75 mmol), and NaI (1.60 g, 10.7 mmol) was stirred at room temperature, while benzyl bromide (25.4 mL, 0.214 mmol) was added in four portions at half hourly intervals. A total of 9 h after the first addition, the mixture was poured onto ice (1.5 kg) and the precipitate was removed by filtration, washed with water, and dried. The crude material was dissolved in CH_2Cl_2 and the solution was filtered through alumina to give **4** (59.55 g, 99%): mp (EtOH) 152–153 °C; ^{1}H NMR (CDCl$_3$) δ 9.13 (dd, $J = 4.2, 1.8$ Hz, 1 H), 8.35 (d, $J = 2.3$ Hz, 1 H), 8.29 (dd, $J = 8.4, 1.8$ Hz, 1 H), 7.83 (d, $J = 2.3$ Hz, 1 H), 7.59 (dd, $J = 8.4, 4.2$ Hz, 1 H), 7.56 (d, $J = 7.6$ Hz, 2 H), 7.40 (dd, $J = 7.6, 7.2$ Hz, 2 H), 7.33 (t, $J = 7.2$ Hz, 1 H), 5.50 (s, 2 H); ^{13}C NMR (CDCl$_3$) δ 155.4, 152.5, 145.6, 142.6, 137.9, 135.4, 128.8, 128.4, 127.8, 127.5, 123.3, 116.3, 103.1, 71.4. Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99. Found: C, 68.51; H, 4.29; N, 10.04.

6-Amino-8-benzyloxyquinoline (5). Iron dust (16.0 g, 0.285 mol) was added to a solution of 4 (8.00 g, 28.5 mmol) and AcOH (16 mL, 0.285 mol) in EtOH–water (5:1, 240 mL) at reflux. After 10 min, the mixture was carefully poured into saturated aqueous $NaHCO_3$ (300 mL). The mixture was filtered through Celite and the filter cake was washed with water (100 mL), EtOH (3 × 50 mL), and CH_2Cl_2 (3 × 100 mL). The combined filtrates were diluted with water (300 mL) and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to give **5** (7.13 g, 100%) as a tan solid: mp 183–185 °C; ^{1}H NMR (CDCl$_3$) δ 8.66 (dd, $J = 4.2, 1.6$ Hz, 1 H), 7.84 (dd, $J = 8.3, 1.6$ Hz, 1 H), 7.48 (dd, $J = 8.1, 1.7$ Hz, 2 H), 7.23–7.39 (m, 3 H), 7.28 (dd, $J = 8.3, 4.2$ Hz, 1 H), 6.51, 6.48 (2 × d, J

= 2.3 Hz, 1 H each), 5.36 (s, 2 H), 3.85 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 155.2, 155.7, 144.8, 136.8, 135.9, 133.5, 130.8, 128.6, 127.8, 127.0, 122.0, 102.6, 100.0, 70.6. Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found C, 76.54; H, 5.61; N, 11.15.

8-Benzyloxy-6-(*tert*-butyloxycarbonylamino)quinoline (6). A mixture of **5** (7.63 g, 30.5 mmol), BOC_2O (8.65 g, 39.6 mmol) and dioxane (70 mL) was stirred at reflux for 2 h. Further BOC_2O (0.86 g, 4.0 mmol) was added and the mixture was heated at reflux for another 1 h. The dioxane was evaporated, the remaining oil was triturated with pentane, and the resulting solid was removed by filtration, dissolved in CH_2Cl_2 and filtered through alumina to give **6** (10.42 g, 98%) as a cream solid: mp 180–181 °C; ^{1}H NMR ($CDCl_3$) δ 8.77 (dd, J = 4.2, 1.6 Hz, 1 H), 7.98 (dd, J = 8.3, 1.6 Hz, 1 H), 7.55 (d, J = 2.1 Hz, 1 H), 7.41 (dd, J = 7.4, 2.2 Hz, 2 H), 7.34 (dd, J = 8.3, 4.2 Hz, 1 H), 7.20–7.29 (m, 3 H), 7.02 (d, J = 2.1 Hz, 1 H), 5.28 (s, 2 H), 1.49 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.6, 152.7, 147.4, 137.2, 136.8, 136.3, 135.2, 129.9, 128.4, 127.7, 127.2, 122.0, 105.8, 103.5, 80.6, 70.6, 28.2. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found C, 71.80; H, 6.31; N, 7.98.

8-Benzyloxy-6-(*tert*-butyloxycarbonylamino)-5-iodoquinoline (7a). A mixture of **6** (1.04 g, 3.0 mmol), NIS (0.70 g, 3.1 mmol) and CH_3CN (10 mL) was stirred at reflux for 30 min. Further NIS (40 mg, 0.18 mmol) was added and the mixture stirred at reflux for a further 30 min. The CH_3CN was evaporated and the residue was taken up in EtOAc (30 mL) and washed with a solution of $Na_2S_2O_5$ and Na_2CO_3 in water (× 3). The aqueous washes were back extracted with EtOAc (× 2). The combined organic extracts were washed with water, dried (brine, $MgSO_4$), filtered through silica gel, and evaporated to give **7a** (1.33 g, 93%), which crystallized from hexane as tan needles: mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 8.79 (dd, J = 4.2, 1.4 Hz, 1 H), 8.32 (dd, J = 8.6, 1.4 Hz, 1 H), 8.29 (s, 1 H), 7.59 (dd, J = 8.0, 1.7 Hz, 2 H), 7.43 (dd, J = 8.6, 4.2 Hz, 1 H), 7.25–7.39 (m, 3 H), 7.24 (br s, 1 H), 5.43 (s, 2 H), 1.57 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.2, 152.4, 148.1, 139.5,

138.9, 138.3, 136.2, 130.7, 128.5, 128.0, 123.4, 103.9, 81.5, 78.1, 71.0, 28.3. Anal. Calcd for $C_{21}H_{21}IN_2O_3$: C, 52.96; H, 4.44; N, 5.88. Found C, 53.18; H, 4.39; N, 5.95.

8-Benzyloxy-6-[*N*-(*tert*-butyloxycarbonyl)-*N*-(3,3-dimethoxypropyl)amino]-5-iodoquinoline (8a). NaH (60% in oil, 92 mg, 2.3 mmol) under nitrogen was washed with pentane (2 × 2 mL), cooled (ice–water) and treated with a solution of **7a** (1.00 g, 2.10 mmol) in DMF (10 mL) over 5 min. The mixture was allowed to warm to room temperature and stir for 30 min, over which time it became bright yellow and effervescence ceased. A solution of 3-bromo-1,1-dimethoxypropane (0.69 g, 3.77 mmol) in DMF (0.5 mL) was added and the mixture was stirred at room temperature for 22 h. The mixture was poured into pH 7.4 phosphate buffer (50 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with water (2 × 50 mL), dried (brine, Na_2SO_4), evaporated, and purified by dry-flash column chromatography (silica gel, 10–90% EtOAc/hexane), to give **8a** (1.00 g, 83%) as a cream powder: mp 120–121 °C; ^{1}H NMR ($CDCl_3$) major rotamer δ 8.94 (br d, J = 2.9 Hz, 1 H), 8.52 (dd, J = 8.6, 1.5 Hz, 1 H), 7.45–7.58 (m, 3 H), 7.25–7.40 (m, 3 H), 6.96 (br s, 1 H), 5.46 (s, 2 H), 4.40 (t, J = 4.7 Hz, 1 H), 3.84 (br ddd, J = 14.6, 7.3, 7.3 Hz, 1 H), 3.33 (ddd, J = 14.6, 8.2, 5.8 Hz, 1 H), 3.28, 3.25 (2 × s, 3 H each), 1.65–1.95 (m, 2 H), 1.23 (br s, 9 H); ^{13}C NMR ($CDCl_3$) major rotamer δ 154.6, 153.6, 149.9, 143.8, 141.3, 139.8, 136.0, 131.2, 128.7, 128.0, 127.0, 123.4, 112.3, 102.9, 93.3, 80.3, 70.9, 53.1, 52.7, 45.4, 31.2, 28.1; $C_{26}H_{31}IN_2O_5$ requires $M^{+\cdot}$ 578.1278. Found 578.1257.

8-Benzyloxy-6-[*N*-(*tert*-butyloxycarbonyl)-*N*-(3-oxopropyl)amino]-5-iodoquinoline (9a). A solution of **8a** (0.75 g, 1.30 mmol), $TsOH.H_2O$ (0.12 g, 0.65 mmol) and water (3.75 mL) in acetone (38 mL) was stirred at reflux for 2.25 h. Most of the acetone was evaporated and the residue was diluted with water (50 mL) and saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated to give **9a** (0.68 g, 99%) as a pale yellow foam; ^{1}H

NMR ($CDCl_3$) major rotamer δ 9.68 (s, 1 H), 8.97 (dd, J = 4.2, 1.5 Hz, 1 H), 8.51 (dd, J = 8.6, 1.5 Hz, 1 H), 7.53 (dd, J = 8.6, 4.2 Hz, 1 H), 7.47–7.55 (m, 2 H), 7.25–7.40 (m, 3 H), 6.87 (br s, 1 H), 5.49 (s, 2 H), 4.17 (br dt, J = 14.5, 7.1 Hz, 1 H), 3.59 (dt, J = 14.5, 6.5 Hz, 1 H), 2.57 (br dd, J = 7.1, 6.5 Hz, 2 H), 1.23 (s, 9 H); ^{13}C NMR ($CDCl_3$) major rotamer δ 200.3, 154.8, 153.4, 150.0, 143.0, 141.0, 139.7, 135.9, 131.0, 128.6, 127.9, 127.0, 123.4, 112.1, 93.1, 80.7, 70.7, 42.9, 42.5, 27.9; $C_{24}H_{25}IN_2O_4$ requires $M^{+\bullet}$ 532.0859. Found 532.0862.

6-[*N*-(3-Acetoxy-2-propenyl)-*N*-(*tert*-butyloxycarbonyl)amino]-8-benzyloxy-5-iodoquinoline (10a). A mixture of **9a** (0.62 g, 1.16 mmol), Et_3N (0.40 mL, 2.87 mmol), Ac_2O (0.25 mL, 2.65 mmol), DMAP (14 mg, 0.11 mmol), and THF (12 mL) was stirred at reflux for 2 h. Further Et_3N (0.80 mL, 5.74 mmol), Ac_2O (0.50 mL, 5.3 mmol), and DMAP (10 mg, 0.08 mmol) were added and heating was continued for a further 2 h. The solvent was evaporated, and the residue was diluted with pH 7.4 phosphate buffer (50 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with water (50 mL), dilute aqueous $NaHCO_3$ (50 mL), and water (50 mL) before being dried (brine, Na_2SO_4), and evaporated. The residue was purified by dry-flash column chromatography (silica gel, 10–80% EtOAc–hexane) to give **10a** (0.54 g, 81%) as a white foam, which contained a 1:4 mixture of Z and E isomers: ^1H NMR ($CDCl_3$) major rotamer δ 8.94 (br s, 1 H), 7.45–7.55 (m, 3 H), 7.27–7.40 (m, 3 H), 6.84–7.12 (m, 2 H), 5.36–5.58 (m, 2.8 H), 4.91 (ddd, J = 7.6, 6.5, 5.9 Hz, 0.2 H), 4.57 (dd, J = 15.0, 5.9 Hz, 0.2 H), 4.39 (dd, J = 14.7, 6.8 Hz, 0.8 H), 4.06 (dd, J = 15.0, 7.6 Hz, 0.2 H), 3.86 (dd, J = 14.7, 7.9 Hz, 0.8 H), 2.08 (s, 2.4 H), 1.88 (s, 0.6 H), 1.57 (br s, 1.8 H), 1.26 (br s, 7.2 H); ^{13}C NMR ($CDCl_3$) major rotamer δ 167.4, 167.0, 154.5, 149.8, 154.3, 149.8, 153.3, 153.1, 142.8, 140.9, 139.7, 138.8, 139.7, 143.1, 135.8, 130.9, 136.0, 127.8, 126.8, 126.7, 128.4, 123.2, 112.1, 112.0, 109.1, 108.2, 93.5, 93.1, 80.9, 80.4, 70.8, 70.7, 46.4, 42.7, 27.9, 28.1, 20.3, 20.1; $C_{26}H_{27}IN_2O_5$ requires $M^{+\bullet}$ 574.0965. Found 574.0962.

1-(Acetoxymethyl)-5-benzyloxy-3-(*tert*-butyloxycarbonyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (11). A solution of **10a** (0.54 g, 0.94 mmol), AIBN (15 mg, 0.09 mmol), and Bu_3SnH (0.32 g, 1.13 mmol) in benzene (45 mL) was stirred at reflux under nitrogen for 5.5 h. The solvent was evaporated, the residue was triturated with pentane, and the precipitate was collected by filtration to give **11** (0.32 g, 77%), which crystallized from MeOH as fluorescent pale yellow rectangular plates: mp 172–173 °C; ^{1}H NMR ($CDCl_3$) δ 8.82 (dd, J = 4.1, 1.4 Hz, 1 H), 8.14 (dd, J = 8.4, 1.4 Hz, 1 H), 8.07 (br s, 1 H), 7.55 (br s, 2 H), 7.41 (dd, J = 8.4, 4.1 Hz, 1 H), 7.36 (dd, J = 7.3, 7.3 Hz, 2 H), 7.30 (tt, J = 7.3, 2.4 Hz, 1 H), 5.44, 5.39 (2 × d, J = 12.5 Hz, 1 H each), 4.42–4.52 (m, 1 H), 4.05–4.14 (m, 2 H), 3.82–3.93 (m, 2 H), 2.08 (s, 3 H), 1.57 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 155.2, 152.3, 146.9, 142.0 (br), 137.0, 136.3, 131.1, 128.5, 127.9, 127.7, 126.0, 122.1, 113.3 (v. br), 100.4 (br), 81.4 (br), 70.7, 65.8, 52.6, 37.7, 28.4, 20.9. Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.46; H, 6.27; N, 6.30.

5-Benzyloxy-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (12). A mixture of **11** (0.22 g, 0.50 mmol), Cs_2CO_3 (0.42 g, 1.29 mmol), and EtOH–water (2:1, 6 mL) was stirred at reflux for 30 min. The mixture was diluted with EtOAc (30 mL) and dilute aqueous $NaHCO_3$ (50 mL). The separated aqueous phase was extracted with EtOAc (30 mL). The combined extracts were washed with water (3 × 50 mL), dried (brine, Na_2SO_4), and evaporated to give **12** (0.19 g, 95%), which crystallized from MeOH as tiny white needles: mp 170-171 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (br s, 1 H), 7.99 (br d, J = 8.0 Hz, 1 H), 7.91 (br s, 1 H), 7.55 (d, J = 6.6 Hz, 2 H), 7.20–7.40 (m, 4 H), 5.29 (s, 2 H), 4.00–4.22 (m, 2 H), 3.65–3.78 (m, 3 H, H-1), 3.23 (br s, 1 H), 1.56 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.4, 152.5 (br), 146.2 (br), 142.2 (v. br), 136.3, 136.2, 131.3, 128.5, 128.0 (v. br), 127.9, 125.9, 121.6, 114.7 (v. br), 100.4 (br), 81.0 (br), 70.7, 64.6, 52.3, 40.9 (br), 28.4. Anal. Calcd. for $C_{24}H_{26}N_2O_4.H_2O$: C, 67.91; H, 6.65; N, 6.60. Found: C, 68.16; H, 6.47; N, 6.71.

5-Benzyloxy-1-(methylsulfonyloxymethyl)-3-(*tert*-butyloxycarbonyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (13). MsCl (0.06 mL, 0.7 mmol) was added to a cooled (ice–water) solution of **12** (0.17 g, 0.41 mmol) and Et_3N (0.2 mL, 1.4 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred for 30 min. The CH_2Cl_2 was evaporated and the residue was stirred with water (25 mL) for 10 min. The mixture was extracted with EtOAc (2 × 25 mL). The combined extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated to give **13** (0.17 g, 86%), which crystallized from MeOH as tiny cream needles: mp 156–157 °C; ^{1}H NMR ($CDCl_3$) δ 8.80 (dd, *J* = 4.2, 1.4 Hz, 1 H), 8.02 (dd, *J* = 8.7, 1.4 Hz, 1 H), 7.97 (br s, 1 H), 7.55 (br d, *J* = 6.9 Hz, 2 H), 7.41 (dd, *J* = 8.7, 4.2 Hz), 7.25–7.38 (m, 3 H), 5.40 (s, 2 H), 4.46 (dd, *J* = 9.8, 3.7 Hz, 1 H), 3.93–4.24 (m, 4 H), 2.90 (s, 3 H), 1.57 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.6, 152.1, 147.0, 141.0 (v. br), 137.1, 136.1, 130.5, 128.4, 127.9, 127.6 (br), 125.7, 122.3, 112.7 (v. br), 100.3, 81.6 (br), 70.7, 69.9, 52.0, 38.2 (br), 37.4, 28.3. Anal. Calcd for $C_{25}H_{28}N_2O_6S$: C, 61.97; H, 5.82; N, 5.78; S, 6.62. Found: C, 62.15; H, 5.96; N, 5.88; S, 6.54.

5-Benzyloxy-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (14). Method 1. A mixture of **13** (50 mg, 0.10 mmol), LiCl (25 mg, 0.59 mmol), and DMF (0.25 mL) was stirred at 80 °C for 1 h, before ice (3 g) was added. The precipitate was removed by filtration, washed with water, and taken up in EtOAc (20 mL). This solution was washed with water (20 mL), dried (Na_2SO_4), and evaporated to give **14** (39 mg, 89%), which crystallized from MeOH as fluorescent cream needles: mp 178–179 °C; ^{1}H NMR ($CDCl_3$) δ 8.82 (dd, *J* = 4.2, 1.5 Hz, 1 H), 8.05 (br s, 1 H), 7.99 (br d, *J* = 8.4 Hz, 1 H), 7.55 (br s, 2 H), 7.41 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.35 (dd, *J* = 7.3, 7.3 Hz, 2 H), 7.30 (tt, *J* = 7.3, 2.4 Hz, 1 H), 5.42, 5.38 (2 × d, *J* = 12.4 Hz, 1 H each), 4.23 (br d, *J* = 11.7 Hz, 1 H), 4.12 (dd, *J* = 11.7, 8.9 Hz, 1 H), 3.92 (dddd, *J* = 10.1, 8.9, 3.2, 2.6 Hz, 1 H), 3.81 (dd, *J* = 11.1, 3.2 Hz, 1 H), 3.45 (dd, *J* = 11.1, 10.1 Hz, 1 H), 1.56 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.5, 152.3, 146.9, 141.9 (br), 137.1, 136.3, 130.3, 128.5, 127.9, 127.7 (br), 125.6, 122.2, 113.4 (v. br), 100.4 (br), 81.6 (br), 70.8,

53.0, 46.3, 41.1, 28.4. Anal. Calcd. for $C_{24}H_{25}ClN_2O_3$: C, 67.84; H, 5.93; Cl, 8.34; N, 6.59. Found: C, 67.85; H, 5.94; N, 6.68; Cl, 8.26.

8-Benzyloxy-6-[*N*-(*tert*-butyloxycarbonyl)-*N*-(3-chloro-2-propenyl)amino]-5-iodoquinoline (15a). NaH (60% dispersion in oil, 0.26 g, 6.5 mmol) under nitrogen was washed with pentane (3 × 2 mL), cooled (ice–water), and treated with a solution of **7a** (2.80 g, 5.88 mmol) in DMF (28 mL) over 5 min. The cooling bath was removed and the mixture was allowed to stir for 30 min, by which time the solution was deep yellow and effervescence had ceased. 1,3-Dichloropropene (0.98 g, 8.82 mmol) was added and the mixture was stirred for 86 h. The mixture was diluted with water (150 mL) and extracted with EtOAc (4 × 25 mL). The combined extracts were washed with water (3 × 100 mL), dried (brine, Na_2SO_4), and evaporated. The residue was triturated with pentane and the precipitate was collected by filtration to give **15a** (3.02 g, 93%) as a tan powder: mp 115–135 °C containing a 1:1 mixture of *Z* and *E* isomers; ^{1}H NMR ($CDCl_3$) major rotamer δ 8.95 (br s, 1 H), 8.50 (dd, J = 8.4, 2.5 Hz, 1 H), 7.46–7.55 (m, 3 H), 7.27–7.41 (m, 3 H), 6.79–6.96 (m, 1 H), 5.30–6.03 (m, 4 H), 4.54 (dd, J = 15.5, 5.6 Hz, 0.5 H), 4.38 (dd, J = 14.8, 6.8 Hz, 0.5 H), 4.18 (dd, J = 15.5, 6.9 Hz, 0.5 H), 3.79 (dd, J = 14.8, 7.8 Hz, 0.5 H), 1.23–1.82 (m, 9 H); ^{13}C NMR ($CDCl_3$) major rotamer δ 154.7, 155.2, 153.6, 153.3, 150.2, 150.1, 143.2, 142.8, 141.2, 140.2, 136.2, 136.0, 131.13, 131.08, 128.79, 128.73, 128.12, 127.99, 127.2, 126.6, 126.98, 126.90, 123.5, 123.4, 122.0, 121.1, 112.2, 111.9, 93.65, 93.58, 80.90, 80.85, 71.0, 70.9, 48.8, 45.4, 28.4, 28.1. $C_{24}H_{24}ClIN_2O_3$ requires $M^{+\bullet}$ 550.0520, 552.0491. Found 550.0536, 552.0503. Purification of the mother liquors by dry-flash column chromatography (silica gel, 10–60% EtOAc–hexane) gave further **15a** (0.14 g, 4%).

Compound 14 by Method 2. A solution of **15a** (3.00 g, 5.45 mmol), AIBN (89 mg, 0.54 mmol), and Bu_3SnH (1.75 g, 6.0 mmol) in benzene (270 mL) was heated at reflux under nitrogen for 3 h. The benzene was evaporated, the residue was

triturated with pentane, and the precipitate was collected by filtration to give **14** (2.21 g, 95%), identical to the material prepared above.

Compound 14 by Method 3. A mixture of **12** (19 mg, 0.047 mmol), Ph_3P (37 mg, 0.14 mmol) and CH_2Cl_2 (0.4 mL) was treated with CCl_4 (0.05 mL, 0.52 mmol), and the mixture was stirred under nitrogen for 4 h. The mixture was diluted with dilute aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 5 mL). The combined extracts were dried (Na_2SO_4), evaporated, and purified by dry-flash column chromatography (silica gel, 10–90% EtOAc/hexane) to give **14** (20 mg, 100%) identical with the material prepared above.

3-(*tert*-Butyloxycarbonyl)-1-(chloromethyl)-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (16). A cooled (ice–water) mixture of **14** (0.11 g, 0.27 mmol), 10% Pd/C (55 mg), and THF (5 mL) under nitrogen was treated with 25% aqueous NH_4HCO_3 (0.67 mL). The mixture was stirred at 0 °C for 6 h, and was then diluted with EtOAc (20 mL), dried (Na_2SO_4), filtered through Celite, evaporated, and purified by dry-flash column chromatography (silica gel, 10–50% EtOAc/hexane) to give **16** (39 mg, 44%) as a white solid: mp 148–149 °C; ^1H NMR ($CDCl_3$) δ 8.61 (dd, J = 4.2, 1.2 Hz, 1 H), 8.01 (dd, J = 8.5, 1.2 Hz, 1 H), 7.83 (br s, 1 H), 7.41 (dd, J = 8.5, 4.2 Hz, 1 H), 4.26 (dd, J = 11.8, 2.2 Hz, 1 H), 4.14 (dd, J = 11.8, 8.5 Hz, 1 H), 3.93 (dddd, J = 9.8, 8.5, 3.2, 2.2 Hz, 1 H), 3.80 (dd, J = 11.1, 3.2 Hz, 1 H), 3.46 (dd, J = 11.1, 9.8 Hz, 1 H), 1.61 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 153.5, 152.3, 145.3, 142.4 (br), 135.0, 130.6, 124.9, 122.6, 112.4 (v. br), 100.0, 81.7 (br), 53.0, 46.5, 40.9, 28.4. $C_{17}H_{19}ClN_2O_3$ requires $M^{+\bullet}$ 334.1084, 336.1055. Found 334.1081, 336.1058.

5-Benzyloxy-1-(chloromethyl)-3-(5,6,7-trimethoxyindol-2-ylcarbonyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (17a). A suspension of **14** (0.65 g, 1.53 mmol) in dioxane (40 mL) was saturated with HCl, allowed to stand for 1 h, and evaporated. 5,6,7-Trimethoxyindole-2-carboxylic acid (0.38 g, 1.53 mmol), EDCI (0.88 g, 4.6 mmol) and DMA (25 mL) were added to the remaining green–yellow

solid, and the red mixture was stirred at room temperature for 39 h. The mixture was poured into a mixture of ice (60 g) and pH 7.4 phosphate buffer (60 mL). The precipitate was removed by filtration, washed with water, and taken up in EtOAc (60 mL). This solution was washed with water (3 × 50 mL), dried (brine, Na_2SO_4), and evaporated. The remaining oil was triturated with Et_2O. The precipitate was collected by filtration, purified by flash column chromatography (silica gel, EtOAc), and triturated with Et_2O to give **17a** (0.38 g, 44%) as a pale yellow solid: mp 182–184 °C; ^{1}H NMR ($CDCl_3$) δ 9.59 (s, 1 H), 8.84 (dd, J = 4.2, 1.6 Hz, 1 H), 8.37 (s, 1 H), 7.95 (dd, J = 8.5, 1.6 Hz, 1 H), 7.58 (br d, J = 7.2 Hz, 2 H), 7.38 (dd, J = 8.5, 4.2 Hz, 1 H), 7.36 (dd, J = 7.3, 7.2 Hz, 2 H), 7.30 (t, J = 7.3 Hz, 1 H), 6.93 (d, J = 2.2 Hz, 1 H), 6.84 (s, 1 H), 5.48, 5.42 (2 × d, J = 12.5 Hz, 1 H each), 4.69 (dd, J = 10.8, 1.9 Hz, 1 H), 4.57 (dd, J = 10.8, 8.5 Hz, 1 H), 4.06, 3.93, 3.90 (3 × s, 3 H each), 4.02 (dddd, J = 10.3, 8.5, 3.2, 1.9 Hz, 1 H), 3.83 (dd, J = 11.4, 3.2 Hz, 1 H), 3.42 (dd, J = 11.4, 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 160.5, 155.3, 147.8, 150.2, 142.3, 140.6, 138.8, 138.2, 129.5, 125.1, 123.5, 136.4, 130.4, 128.6, 128.0, 127.7, 125.6, 122.3, 115.3, 106.7, 102.3, 97.6, 70.8, 61.4, 61.1, 56.2, 55.1, 45.9, 42.5. $C_{31}H_{28}ClN_3O_5$ requires M+H 558.1796, 560.1766. Found (FAB) 558.1770, 560.1786. Anal. Calcd for $C_{31}H_{28}ClN_3O_5$: C, 66.72; H, 5.06; N, 7.53. Found: C, 66.96; H, 5.36; N, 7.50.

1-(Chloromethyl)-5-hydroxy-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (18a). Method 1. THF (10 mL) then 25% aqueous NH_4HCO_3 (1.1 mL) were added to a cooled (ice–water) mixture of **17a** (0.25 g, 0.45 mmol) and 10% Pd/C (0.13 g) under nitrogen. The mixture was stirred at 0 °C for 7.5 h, and was then filtered through Celite. The Celite was washed with a solution of concentrated HCl (2 mL) and MeOH (40 mL) and then with CH_2Cl_2–MeOH (3:1, 40 mL). The combined filtrates were diluted with water (40 mL) and CH_2Cl_2 (30 mL) and neutralized with pH 7.4 phosphate buffer. The lower layer was separated then diluted with MeOH (20 mL) and warmed to dissolve the suspended solid. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were combined, washed with water (100 mL), dried

(Na_2SO_4), and concentrated to a volume of 20 mL. The concentrate was diluted with MeOH (20 mL) and was concentrated to a volume of 10 mL. The precipitate was removed by filtration and washed with MeOH to give **18a** (0.14 g, 66%) as a pale yellow microcrystalline solid: mp > 230 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.50 (d, J = 2.1 Hz, 1 H), 10.03 (br s, 1 H), 8.76 (dd, J = 4.1, 1.3 Hz, 1 H), 8.40 (dd, J = 8.4, 1.3 Hz, 1 H), 7.97 (s, 1 H), 7.56 (dd, J = 8.4, 4.1 Hz, 1 H), 7.09 (d, J = 2.1 Hz, 1 H), 6.97 (s, 1 H), 4.77 (dd, J = 11.0, 9.3 Hz, 1 H), 4.48 (dd, J = 11.0, 2.0 Hz, 1 H), 4.25 (dddd, J = 9.3, 3.9, 3.3, 2.0 Hz, 1 H), 4.03 (dd, J = 10.6, 3.3 Hz, 1 H), 3.93, 3.82, 3.80 (3 × s, 3 H each), 3.89 (dd, J = 10.6, 3.9 Hz, 1 H); ^{13}C NMR ($(CD_3)_2SO$) δ 160.3, 153.9, 146.3, 149.1, 142.7, 139.9, 139.0, 136.0, 130.7, 125.4, 124.8, 123.1, 131.6, 122.4, 114.6, 106.2, 102.8, 98.0, 61.0, 60.9, 55.9, 55.0, 47.6, 40.5. Anal. Calcd for $C_{24}H_{22}ClN_3O_5$: C, 61.61; H, 4.74; Cl, 7.58; N, 8.98. Found: C, 61.50; H, 4.98; N, 8.84.

Compound 18a by Method 2. A solution of **16** (0.14 g, 0.43 mmol) in dioxane (9 mL) was saturated with HCl, allowed to stand for 1 h, and evaporated. 5,6,7-Trimethoxyindole-2-carboxylic acid (0.11 g, 0.43 mmol), EDCI (0.25 g, 1.28 mmol) and DMA (5 mL) were added to the remaining yellow solid, and the red mixture was stirred at room temperature for 22 h. The mixture was poured into a mixture of ice (20 g) and pH 7.4 phosphate buffer (20 mL). The precipitate was removed by filtration, washed with water, and taken up in CH_2Cl_2–MeOH (2:1, 30 mL). The CH_2Cl_2 was boiled off, the remaining mixture was cooled in ice, and the precipitate was removed by filtration to give **18a** (18 mg, 9%) identical to the material prepared above.

Similarly were prepared:

1-(Chloromethyl)-3-({5-[2-(dimethylamino)ethoxy]-5-hydroxyindol-2-yl}carbonyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (18b).
A suspension of **14** (0.20 g, 0.47 mmol) in cooled (0 °C) dioxane (5 mL) was saturated with HCl, allowed to warm to r.t. over 2 h and evaporated. 5-[2-

(Dimethylamino)ethoxy]-1-*H*-indole-2-carboxylic acid hydrochloride (0.13 g, 0.47 mmol) [Milbank et al., J. Med. Chem., 1999, 42, 649], EDCI (0.27 g, 1.42 mmol) and DMA (3 mL) were added to the remaining yellow solid, and the red mixture was stirred at r.t. for 20 h. The mixture was partitioned between EtOAc and 5% $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (x3). The EtOAc extracts were dried (brine, Na_2SO_4). Flash chromatography (Alumina, EtOAc/MeOH; 49:1, then 9:1) gave 2-[(2-{[5-(benzyloxy)-1-(chloromethyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*f*]quinolin-3-yl]carbonyl}-1*H*-indol-5-yl)oxy]-*N*,*N*-dimethylethanamine (**17b**) (0.22 g, 84%) as a yellow solid: mp 176-179 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.68 (s, 1 H), 8.79 (dd, *J* = 4.1, 1.5 Hz, 1 H), 8.41 (dd, *J* = 8.6, 1.5 Hz, 1 H), 8.29 (s, 1 H), 7.56 (m, 3 H), 7.40 (m, 4 H), 7.17 (d, *J* = 2.3 Hz, 1 H), 7.11 (d, *J* = 1.5 Hz, 1 H), 6.92 (dd, *J* = 9.0, 2.4 Hz, 1 H), 5.32 (s, 2 H), 4.82 (dd, *J* = 10.7, 9.6 Hz, 1 H), 4.58 (dd, *J* = 10.9, 2.1 Hz, 1 H), 4.32 (m, 1 H), 4.05 (t, *J* = 5.7 Hz, 2 H), 4.04 (m, 1 H), 3.93 (dd, *J* = 11.2, 6.9 Hz, 1 H), 2.65 (t, *J* = 5.8 Hz, 2 H), 2.23 (s, 6H); ^{13}C NMR [$(CD_3)_2SO$] δ 160.3, 154.5, 153.0, 147.3, 142.3, 137.4, 136.7, 131.6, 131.3, 130.6, 128.4, 127.9, 127.7, 127.4, 125.1, 122.4, 116.2, 116.0, 113.1, 105.5, 103.1, 102.0, 70.0, 66.9, 66.2, 57.8, 54.9, 47.7, 45.5, 40.7.

THF (8 mL) then HCO_2NH_4 (0.23 g, 3.6 mmol) in H_2O (1 mL) were added to cooled (0 °C) mixture of **17b** (0.20 g, 0.36 mmol) and 10% Pd/C (0.1 g) under N_2. The mixture was stirred at 0 °C for 14 h, and was then filtered through Celite. The Celite was washed with CH_2Cl_2/H_2O. The aqueous layer was extracted with CH_2Cl_2 (x3). The CH_2Cl_2 extracts were dried (brine, Na_2SO_4) and passed through a short plug of silica gel to give **18b** (0.16 g, 93%) as a yellow solid: mp 209-215 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.66 (s, 1 H), 10.02 (bs, 1 H), 8.76 (dd, *J* = 4.1, 1.4, 1 H), 8.41 (dd, *J* = 8.5, 1.3, 1 H), 8.07 (s, 1 H), 7.56 (dd, *J* = 8.5, 4.1, 1 H), 7.40 (d, *J* = 8.9, 1 H), 7.17 (d, *J* = 2.2, 1 H), 7.11 (d, *J* = 1.2, 1 H), 6.93 (dd, *J* = 8.9, 2.3, 1 H), 4.82 (dd, *J* = 10.7, 9.6, 1 H), 4.57 (dd, *J* = 11.0, 2.1, 1 H), 4.29 (m, 1 H), 4.06 (t, *J* = 5.9, 2 H), 4.04 (m, 1 H), 3.91 (dd, *J* = 11.1, 7.2, 1 H), 2.64 (t, *J* = 5.8, 2 H), 2.28 (s, 6 H); ^{13}C NMR [$(CD_3)_2SO$] δ 160.3, 153.9, 153.0, 146.4, 142.8,

136.1, 131.6, 130.7, 127.4, 124.8, 124.7, 122.5, 116.0, 114.6, 113.1, 105.5, 103.1, 103.0, 66.1, 57.8, 54.9, 47.7, 45.5, 40.7.

1-(Chloromethyl)-3-((2*E*)-3-{4-[2-(dimethylamino)ethoxy]phenyl}-2-propenoyl)-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (18c).

A suspension of **14** (0.20 g, 0.47 mmol) in cooled (0 °C) dioxane (5 mL) was saturated with HCl, allowed to warm to r.t. over 1 h and evaporated. (*E*)-4-[2-(Dimethylamino)ethoxy]cinnamic acid hydrochloride (0.13 g, 0.47 mmol) [Atwell et al., J. Med. Chem., 1999, 42, 3400], EDCI (0.27 g, 1.42 mmol) and DMA (3 mL) were added to the remaining yellow solid, and the red mixture was stirred at r.t. for 30 h. The mixture was partitioned between CH_2Cl_2 and 5% $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (x3). The CH_2Cl_2 extracts were dried (brine, Na_2SO_4). Flash chromatography (Alumina, EtOAc/MeOH; 49:1, then 24:1) gave 2-(4-{(1*E*)-3-[5-(benzyloxy)-1-(chloromethyl)-1,2-dihydro-3*H*-pyrrolo[3,2-*f*]quinolin-3-yl]-3-oxo-1-propenyl}phenoxy)-*N*,*N*-dimethylethanamine (**17c**) (0.18 g, 70%) as a yellow solid : mp 172-175 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.76 (dd, *J* = 4.1, 1.4, 1 H), 8.47 (bs, 1 H), 8.35 (dd, *J* = 8.5, 1.4, 1 H), 7.76 (d, *J* = 8.7, 2 H), 7.67 (d, *J* = 15.3, 1 H), 7.58 (d, *J* = 7.3, 2 H), 7.54 (dd, *J* = 8.5, 4.1, 1 H), 7.44 (t, *J* = 7.2, 2 H), 7.37 (t, *J* = 7.2, 1 H), 7.08 (d, *J* = 15.3, 1 H), 7.02 (d, *J* = 8.7, 2 H), 5.31 (s, 2 H), 4.55 (dd, *J* = 10.7, 9.5, 1 H), 4.44 (dd, *J* = 10.9, 2.5, 1 H), 4.30 (m, 1 H), 4.11 (t, *J* = 5.8, 2 H), 3.99 (dd, *J* = 11.0, 3.0, 1 H), 3.91 (dd, *J* = 11.2, 7.2, 1 H), 2.64 (t, *J* = 5.7, 2 H), 2.23 (s, 6 H); ^{13}C NMR [$(CD_3)_2SO$] δ 164.1, 160.1, 154.6, 147.1, 142.6, 142.2, 137.2, 136.7, 131.1, 130.1, 128.3, 127.83, 127 78, 127.3, 125.1, 122.3, 116.9, 115.7, 114.7, 101.6, 70.0, 65.9, 57.5, 52.9, 47.8, 45.4, 40.1.

A solution of **17c** (0.56 g, 1.03 mmol) was dissolved in CF_3COOH (15 mL) and refluxed for 48 h. CF_3COOH was evaporated and the residue was partitioned between CH_2Cl_2 and cold 5% $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (x3). The CH_2Cl_2 extracts were dried (brine, Na_2SO_4). Flash chromatography (CH_2Cl_2/MeOH/NH_3; 95:5:trace) gave **18c** (0.16 g, 34%) as a

yellow solid: mp 174-180 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.96 (bs, 1 H), 8.73 (dd, J = 4.0, 1.3, 1 H), 8.36 (dd, J = 8.4, 1.3, 1 H), 8.18 (bs, 1 H), 7.77 (d, J = 8.7, 2 H), 7.66 (d, J = 15.2, 1 H), 7.54 (dd, J = 8.5, 4.1, 1 H), 7.08 (d, J = 15.4, 1 H), 7.02 (d, J = 8.7, 2 H), 4.54 (dd, J = 10.7, 9.5, 1 H), 4.44 (dd, J = 11.0, 2.5, 1 H), 4.28 (m, 1 H), 4.11 (t, J = 5.7, 2 H), 4.00 (dd, J = 11.1, 3.1, 1 H), 3.88 (dd, J = 11.0, 7.4, 1 H), 2.64 (t, J = 5.8, 2 H), 2.22 (s, 6 H).

1-(Chloromethyl)-3-[(5-methoxyindol-2-yl)carbonyl]-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (18d).

A suspension of **14** (0.10 g, 0.24 mmol) in dioxane (15 mL) was saturated with HCl, stirred at r.t. for 5 h and evaporated. 5-Methoxy-1-*H*-indole-2-carboxylic acid (0.054 g, 0.28 mmol), EDCI (0.23 g, 1.17 mmol) and DMA (5 mL) were added to the remaining yellow solid, and the red mixture was stirred at r.t. for 52 h. The mixture was partitioned between CH_2Cl_2 and cold 5% $KHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (x3). The CH_2Cl_2 extracts were dried (brine, Na_2SO_4). Flash chromatography (EtOAc/petroleum ether; 7:3) gave 5-(benzyloxy)-1-(chloromethyl)-3-[(5-methoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (**17d**) (0.11 g, 98%) as a yellow solid : mp 186-189 °C; ^{1}H NMR ($CDCl_3$) δ 9.55 (s, 1 H), 8.88 (dd, J = 4.2, 1.7, 1 H), 8.37 (s, 1 H), 7.99 (dd, J = 8.3, 1.6, 1 H), 7.56 (d, J = 7.3, 2 H), 7.42 (dd, J = 8.3, 4.1, 1 H), 7.33 (m, 4 H), 7.10 (d, J = 2.3, 1 H), 6.99 (m, 2 H), 5.48 (d, J = 12.5, 1 H), 5.42 (d, J = 12.6, 1 H), 4.74 (dd, J = 10.9, 2.0, 1 H), 4.61 (dd, J = 10.6, 8.7, 1 H), 4.05 (m, 1 H), 3.85 (s, 3 H), 3.84 (dd, J = 11.2, 4.1, 1 H), 3.45 (dd, J = 11.0, 10.5, 1 H); ^{13}C NMR ($CDCl_3$) δ 160.7, 155.4, 154.7, 147.9, 142.4, 138.4, 136.4, 131.4, 130.5, 130.2, 128.6, 128.2, 128.0, 127.7, 125.2, 122.4, 117.0, 115.4, 112.7, 106.2, 102.5, 102.4, 70.9, 55.7, 55.2, 45.9, 42.6.

THF (6 mL) then HCO_2NH_4 (0.14 g, 2.21 mmol) in H_2O (0.7 mL) were added to cooled (0 °C) mixture of **17d** (0.11 g, 0.22 mmol) and 10% Pd/C (0.05 g) under N_2. The mixture was stirred at 0 °C for 5 h, and was then filtered through Celite. The Celite was washed with CH_2Cl_2/H_2O. The aqueous layer was extracted with

CH_2Cl_2 (x3). The CH_2Cl_2 extracts were dried (brine, Na_2SO_4) and CH_2Cl_2 evaporated. Precipitation from CH_2Cl_2/MeOH gave **18d** (0.077 g, 89%) as a grey solid: mp 224-227 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.66 (s, 1 H), 10.02 (bs, 1 H), 8.77 (dd, J = 4.1, 1.3, 1 H), 8.41 (dd, J = 8.4, 1.4, 1 H), 8.07 (s, 1 H), 7.57 (dd, J = 8.4, 4.1, 1 H), 7.40 (d, J = 9.0, 1 H), 7.16 (d, J = 2.4, 1 H), 7.12 (d, J = 1.6, 1 H), 6.92 (dd, J = 8.9, 2.3, 1 H), 4.82 (dd, J = 10.8, 9.4, 1 H), 4.57 (dd, J = 11.0, 2.3, 1 H), 4.30 (m, 1 H), 4.04 (dd, J = 11.1, 3.3, 1 H), 3.91 (dd, J = 11.1, 7.2, 1 H), 3.78 (s, 3 H).

1-(Chloromethyl)-3-[(2*E*)-3-(4-methoxyphenyl)-2-propenoyl]-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (18e).

A suspension of **16** (0.10 g, 0.30 mmol) in dioxane (5 mL) was saturated with HCl, stirred at r.t. over 5 h and evaporated. 4-Methoxycinnamic acid (predominantly *trans*) (0.064 g, 0.36 mmol), EDCI (0.29 g, 1.50 mmol) and DMA (3 mL) were added to the remaining yellow solid, and the red mixture was stirred at r.t. for 3 h. The mixture was partitioned between CH_2Cl_2 and cold 5% $KHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (x3). The CH_2Cl_2 extracts were dried (brine, Na_2SO_4). Flash chromatography (CH_2Cl_2/MeOH; 93:7) followed by recrystallisation (CH_2Cl_2/Et_2O) gave **18e** (0.02 g, 17%) as a yellow solid: mp 208-211 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.96 (bs, 1 H), 8.73 (d, J = 3.3, 1 H), 8.35 (d, J = 7.7, 1 H), 8.18 (bs, 1 H), 7.78 (d, J = 8.7, 2 H), 7.67 (d, J = 15.3, 1 H), 7.54 (dd, J = 8.5, 4.1, 1 H), 7.08 (d, J = 15.4, 1 H), 7.01 (d, J = 8.7, 2 H), 4.54 (dd, J = 10.3, 9.5, 1 H), 4.45 (m, 1 H), 4.27 (m, 1 H), 3.99 (dd, J = 11.1, 3.2, 1 H), 3.88 (dd, J = 11.1, 7.3, 1 H), 3.82 (s, 3 H). $C_{22}H_{20}ClN_2O_3$ requires M+H 395.1163, 397.1133. Found (FAB) 395.1161, 397.1169.

1-(Chloromethyl)-3-[(2*E*)-3-(3-hydroxy-4-methoxyphenyl)-2-propenoyl]-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline (18f).

A suspension of **16** (0.10 g, 0.30 mmol) in dioxane (5 mL) was saturated with HCl, stirred at r.t. over 5 h and evaporated. 3-Hydroxy-4-methoxycinnamic acid (predominantly *trans*) (0.070 g, 0.36 mmol), EDCI (0.29 g, 1.50 mmol) and DMA

(3 mL) were added to the remaining yellow solid, and the red mixture was stirred at r.t. for 3 h. The mixture was partitioned between CH_2Cl_2 and cold 5% $KHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (x3). The CH_2Cl_2 extracts were dried (brine, Na_2SO_4). Flash chromatography (CH_2Cl_2/MeOH; 93:7) followed by recrystallisation (CH_2Cl_2/Et_2O) gave **18f** (0.01 g, 8%) as a yellow solid: mp 215-218 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.96 (bs, 1 H), 9.13 (s, 1 H), 8.73 (dd, J = 4.1, 1.4, 1 H), 8.36 (dd, J = 8.5, 1.4, 1 H), 8.17 (bs, 1 H), 7.57 (d, J = 15.3, 1 H), 7.54 (dd, J = 8.5, 4.1, 1 H), 7.25 (d, J = 2.0, 1 H), 7.20 (dd, J = 8.4, 2.0, 1 H), 6.99 (d, J = 8.1, 1 H), 6.96 (d, J = 15.0, 1 H), 4.54 (dd, J = 10.5, 9.4, 1 H), 4.44 (dd, J = 11.1, 2.6, 1 H), 4.00 (dd, J = 11.2, 3.3, 1 H), 3.88 (dd, J = 11.1, 7.5, 1 H), 3.83 (s, 3H). $C_{22}H_{19}{}^{35}ClN_2O_4$ requires M+H 411.1112. Found (FAB) 411.1127.

Example B. Preparation of 5-amino-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-f]quinoline **27** by the method of Scheme 4.

8-Nitroquinoline-6-carboxylic acid (19). This was prepared by the reported method [Jung et al., Eur. Pat. Appln. EP 581500 (1994); Chem Abstr, 1994, 122, 205125] in 41% yield: mp (EtOAc) 258-263 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.80 (v br, 1 H), 9.16 (dd, J = 4.3, 1.7 Hz, 1 H), 8.96 (d, J = 1.7 Hz, 1 H), 8.80 (dd, J = 8.4, 1.6 Hz, 1 H), 8.63 (d, J = 1.7 Hz, 1 H), 7.84 (dd, J = 8.4, 4.2 Hz, 1 H).

6-(*tert.*-Butyloxycarbonylamino)-8-nitroquinoline (20) A mixture of **19** (4.82 g, 22.1 mmol), DPPA (6.99 g, 25.4 mmol) and Et_3N (3.69 mL, 26.5 mmol) in anhydrous t-BuOH (60 mL) was heated at reflux under N_2 for 8 h. The mixture was concentrated under reduced pressure, and the residue was partitioned between CH_2Cl_2 and 10% aqueous $KHCO_3$. The organic phase was washed with 10% aqueous $KHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure, then chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc (17:3), followed by sequential crystallisation from MeOH/H_2O andCH_2Cl_2/petroleum ether gave **20** (3.82 g, 60%): mp 134-135 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.09 (s, 1 H), 8.87 (dd, J

= 4.1, 1.5 Hz, 1 H), 8.47 (dd, J = 8.5, 1.6 Hz, 1 H), 8.33 (d, J = 1.9 Hz, 1 H), 8.25 (d, J = 2,2 Hz, 1 H), 7.65 ,m(dd, J = 2.2 Hz, 1 H), 7.65 (dd, J = 8.5, 4.2 Hz, 1 H), 1.53 (s, 9 H). Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 58.39; H, 5.21; N, 14.65%.

8-Amino-6-(*tert.*-butyloxycarbonylamino)quinoline (21)A solution of **20** (3.30 g, 11.4 mmol) in MeOH (50 mL) was hydrogenated over 10% Pd/C at 50 psi for 3 h. The resulting crude product was filtered through a column of silica gel in EtOPAc to give **21** (2.71 g, 92%): mp (i-Pr_2O/petroleum ether) 131-132 °C; ^1H NMR [$(CD_3)_2SO$] δ 9.39 (s, 1 H), 8.54 (dd, J = 4.1, 1.6 Hz, 1 H), 8.01 (dd, J = 8.3, 1.5 Hz, 1 H), 7.36 (dd, J = 8.3, 4.1 Hz, 1 H), 7.24 (d, J = 2.0 Hz, 1 H), 6.97 (d, J = 2.1 Hz, 1 H), 5.90, 5.88 (2xs, 2 H, NH_2), 1.50 (s, 9 H). Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.60; H, 6.77; N, 16.19%.

6-(tert.-Butyloxycarbonyl)-8-(1.3-dioxo-1,3-dihydro-2H-isoindol-2-yl)quinoline (22). A mixture of **21** (1.53 g, 5.90 mmol), phthalic anhydride (1.05 g, 7.09 mmol) and DMAP (36 mg, 5 mol%), in anhydrous pyridine (15 mL) was heated with stirring at 80 °C for 1 h. The mixture was concentrated under reduced pressure, then AcOH (10 mL) and Ac_2O (5 ml) were added and the mixture was stirred at 80 °C for a further 45 min. Concentration under reduced pressure, followed by addition of aqueous $KHCO_3$, gave a solid that was chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc (4:1) gave a crude product that was crystallized from CH_2Cl_2/iPr_2O to give **22** (2.09 g): mp 217-218 °C (dec.); ^1H NMR [$(CD_3)_2SO$] δ 10.00 (s, 1 H), 8.67 (d, J = 3.2 Hz, 1 H), 8.39 (d, J = 8.1 Hz, 1 H, H-4), 8.24 (s, 1 H), 8.80-7.89 (m, 5 H), 7.53 (dd, J = 8.3, 4.1 Hz, 1 H), 1.53 (s, 9 H). Anal. Calcd. for $C_{22}H_{19}N_3O_4$: C, 67.85; H, 4.92; N, 10.79. Found: C, 67.87; H, 4.94; N, 10.87%.

5-Bromo-6-(*tert.*-butyloxycarbonylamino)-8-(1,3-dioxo-1,3-dihydro-1H-isoindol-2-yl)quinoline (23). A mixture of **22** (1.79 g, 4.6 mmol) and NBS (0.98 g, 5.5 mmol) in anhydrous CH_3CN (50 mL) was stirred at reflux for 45 min, then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, and

the solution was washed with aqueous $Na_2S_2O_5$/$NaHCO_3$ and water (2x), dried (Na_2SO_4) and concentrated to dryness. The residue was chromatographed on silica gel, and elution with CH_2Cl_2/EtOAc (3:2) gave a crude product that was crystallized from EtOAc/iPr_2O to **23** (1.91 g, 89%): mp 210-211 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 9.19 (s, 1 H), 8.85 (dd, J = 4.1, 1.4 Hz, 1 H), 8.65 (dd, J = 8.6, 1.4 Hz, 1 H), 8.21 (s, 1 H), 8.07-7.92 (m, 4 H), 7.75 (dd, J = 9.7, 4.2 Hz, 1 H), 1.50 (s, 9 H). Anal. Calcd. for $C_{22}H_{18}BrN_3O_4$: C, 56.42; H, 3.87; N, 8.98; Br, 17.06. Found: C, 56.49; H, 4.04; N, 8.86; Br, 16.87%.

5-Bromo-6-[N-(*tert.*-butyloxycarbonyl)-*N*-(3-chloro-2-propen-1-yl)amino]-8-(1,3-dioxo-1,3-dihydro-1H-isoindol-2-yl)quinoline (24). A solution of **23** (1.82 g, 3.89 mmol) in anhydrous DMF (20 mL) was treated at 0 °C under N_2 with NaH (0.20 g, 5.00 mmol, 60% in oil), and then stirred at 25 °C for 45 min. The mixture was then cooled to 0 °C and 1,3-dichloropropene (1.11 mL, 11.7 mmol) was added. The reaction mixture was warmed to 25 °C, stirred for 4 h, and then diluted with CH_2Cl_2 (200 mL). The solution was washed with 10% aqueous $KHCO_3$ and water (2x), then dried (Na_2SO_4) and concentrated under high vacuum at 25 °C. The residue was chromatographed on silica gel, eluting with CH_2Cl_2 then CH_2Cl_2/EtOAc (17:3) to give **24** (1.62 g, 77%) as a foam that was used directly; ^{1}H NMR [$(CD_3)_2SO$] (mixture of rotamers of E and Z alkenes) δ 8.94 (d, J = 4.0 Hz, 1 H), 8.73 (d, J = 8.6 Hz, 1 H), 8.12-7.93 (m, 5 H), 7.80 (dd, J = 8.6, 4.2 Hz, 1 H), 6.50-6.35 (m, 1 H), 6.21-6.02 (m, 1 H), 4.62-4.06 (m, 2 H), 1,51, 1.32 (2xs, 9 H). Anal. Calcd. for $C_{25}H_{21}BrClN_3O_4.2H_2O$: C, 51.87; H, 4.35; N, 7.26. Found: C, 51.69; H, 3.87; N, 6.86%.

3-(*tert.*-Butyloxycarbonyl)-1-(chloromethyl)-5-(1,3-dioxo-1,3-dihydro-*1H*-isoindol-2-yl)-2,3-dihydro-*1H*-pyrrolo[3,2-f]quinoline (25). A mixture of **24** (1.96 g, 3.61 mmol) and catalytic AIBN (60 mg, 10 mol%) in anhydrous benzene (20 mL) was treated with Bu_3SnH (1.16 mL, 4.33 mmol) and heated at reflux under N_2 for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc

(17:3), followed by crystallisation from CH_2Cl_2/petroleum ether gave **25** (1.28 g, 76%): mp 163-165 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.70 (dd, J = 4.1, 1.3 Hz, 1 H), 8.51 (dd, J = 8.6, 1.4 Hz, 1 H), 8.45 (v br, 1 H), 8.06-7.90 (m, 4 H), 7.57 (dd, J = 8.5, 4.1 Hz, 1 H), 4.44-4.34 (m, 1 H), 4.29 (t, J = 10.5 Hz, 1 H), 4.19-3.99 (m, 3 H), 1.54 (s, 9 H). Anal. Calcd. for $C_{25}H_{22}ClN_3O_4$: C, 64.72; H, 4.78; N, 9.06. Found: C, 64.76; H, 4.92; N, 9.03%.

1-(Chloromethyl)-5-(1,3-dioxo-1,3-dihydro-*1H*-isoindol-2-yl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-1H-pyrrolo[3,2-f]quinoline (26). A solution of **25** (500 mg, 108 mmol) in dioxane at 10 °C was saturated with HCl gas, allowed to stand at 20 °C for 1 h, then evaporated to dryness under reduced pressure below 30 °C. 5,6,7-Trimethoxyindole-2-carboxylic acid (298 mg, 1.19 mmol), EDCI (518 mg, 2.70 mmol) and anhydrous DMA (10 mL) were then added, and the mixture was stirred at 20 °C for 3 h. Addition of 10% aqueous $KHCO_3$ precipitated a solid that was chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc (1:1), followed by crystallisation from EtOAc/iPr_2O, gave 1-(chloromethyl)-5-(phthalimido)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-*1H*-pyrrolo[3,2-f]quinoline **26** (392 mg, 61%): mp 189-191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.54 (s, 1 H), 8.77 (dd, J = 4.1, 1.4 Hz, 1 H), 8.75 (s, 1 H), 8.59 (dd, J = 8.5, 1.4 Hz, 1 H), 8.08-7.92 (m, 4 H), 7.61 (dd, J = 8.5, 4.2 Hz, 1 H), 7.14 (d, J = 1.7 Hz, 1 H), 6.98 (s, 1 H), 4.89 (dd, J = 10.8, 9.7 Hz, 1 H), 4.61 (dd, J = 11.0, 2.3 Hz, 1 H), 4.55-4.44 (m, 1 H), 4.20-4.05 (m, 2 H), 3.94, 3.83, 3.81 (3xs, 3x3H). Anal. Calcd. for $C_{32}H_{25}ClN_4O_6$: C, 64.37; H, 4.22; N, 9.39. Found: C, 64.04; H, 4.28; N, 9.29%.

5-Amino-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-*1H*-pyrrolo[3,2-f]quinoline (27). A solution of **26** (160 mg, 0.27 mmol) in CH_2Cl_2 (6 mL) was was diluted with EtOAc (8 mL) and treated immediately with hydrazine monohydrate (155 μL, 3.19 mmol). The reaction mixture was stirred at 25 °C for 2 h, then diluted with CH_2Cl_2 (40 mL), washed with 10% aqueous Na_2CO_3 (2x) and saturated aqueous NaCl (2x), dried (Na_2SO_4) and

concentrated under reduced pressure below 30 °C. Chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (1:1) gave **27** (81 mg, 65%): mp 225-227 °C; ^1H NMR [$(CD_3)_2SO$] δ 11.44 (s, 1 H), 8.63 (dd, J = 4.1, 1.4 Hz, 1 H), 8.25 (dd, J = 8.5, 1.4 Hz, 1 H), 7.82 (s, 1 H), 7.47 (dd, J = 8.5, 4.1 Hz, 1 H), 7.05 (d, J = 1.2 Hz, 1 H), 6.99 (s, 1 H), 6.18, 6.16 (2xs, 2 H), 4.70 (dd, J = 10.8, 9.1 Hz, 1 H), 4.43 (dd, J = 11.0, 1.8 Hz, 1 H), 4.16-4.08 (m, 1 H), 3.97 (dd, J = 11.0, 3.3 Hz, 1 H), 3.94, 3.82, 3.80 (3xs, 3x3 H), 3.76 (dd, J = 10.0, 7.8 Hz, 1 H). Anal. Calcd. for $C_{24}H_{23}ClN_4O_4$: C, 61.74; H, 4.96; N, 12.00. Found: C, 61.51; H, 5.04; N, 11.69%.

Example C: Preparation of 5-(2-aminoethylamino)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole dihydrochloride **29** by the method of Scheme 5. A mixture of 5-amino-1-(chloromethyl)-3-[5,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole **28** [Atwell et al., J. Org. Chem. 1998, 63, 9414] (252 mg, 0.54 mmol), *N*-(*tert*-butyloxycarbonyl)aminoacetaldehyde (430 mg, 2.70 mmol) TsOH (10 mg) and microwave-dried powdered A4 molecular sieves (3 g) in DMA (3 mL) and MeOH (0.5 mL) was stirred at 20 °C under N_2 with the exclusion of light for 48 h. $NaBH_3CN$ (170 mg, 2.70 mmol) was added and the mixture was stirred for a further 4 h at 20 °C, then poured into water. After prolonged cooling the resulting oily precipitate was collected and extracted with CH_2Cl_2. Following filtration the solution was washed with water, dried (Na_2SO_4) and then concentrated under reduced pressure below 30 °C. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/EtOAc (9:2), to provide material that was precipitated from a CH_2Cl_2 solution with petroleum ether at 20 °C to give 5-[2-(*tert*-butyloxycarbonylamino)ethylamino]-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (132 mg, 40%), mp 110-115 °C. ^1H NMR [$(CD_3)_2SO$] δ 11.45 (s, 1 H), 8.09 (d, J = 8.5 Hz, 1 H), 7.79 (d, J = 8.3 Hz, 1 H), 7.53-7.26 (underlying v br s, 1 H), 7.49 (t, J = 7.7 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.04 (s, 1 H), ca 7.07-7.00 (obscured signal, 1 H), 6.97 (s, 1 H), 6.28 (br s, 1 H), 4.68 (t, J = 9.8 Hz, 1 H), 4.45 (dd, J = 11.0, 1.4 Hz, 1 H), 4.17-4.07 (m, 1

H), 3.98 (dd, J = 11.0, 3.0 Hz, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.76 (dd, J = 10.7, 8.0 Hz, 1 H), ca 3.3 (br s, obscured by H_2O signal but visible after D_2O exchange, 2 H), 3.18 (br s, 2 H), 1.39 (s, 9 H). Anal. Calcd. for $C_{32}H_{37}ClN_4O_6$: C, 63.1; H, 6.1; N, 9.2; Cl, 5.8. Found: C, 63.0; H, 6.1; N, 9.4; Cl, 5.7%.

A solution of the above compound (122 mg, 0.20 mmol) in dioxane (3 mL) was treated with HCl-saturated EtOAc (3 mL), and the mixture was stood at 20 °C for 1 h. Excess EtOAc was then added to complete separation of the product, which was collected and recrystallised from MeOH/EtOAc/petroleum ether/HCl to give 5-(2-aminoethylamino)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole dihydrochloride **29** (86 mg, 74%), mp >200 °C. ^{1}H NMR [free base in $(CD_3)SO$] δ 11.46 (br s, 1 H), 8.17 (d, J = 8.6 Hz, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), ca. 7.5-7.3 (underlying v br s, 1 H), 7.49 (t, J = 7.6 Hz, 1 H), 7.32 (t, J = 7.7 Hz, 1 H), 7.04 (s, 1 H), 6.97 (s, 1 H), 6.28 (t, J = 5.0 Hz, 1 H), 4.67 (t, J = 9.5 Hz, 1 H), 4.45 (dd, J = 11.0, 1.3 Hz, 1 H), 4.19-4.07 (m, 1 H), 3.98 (dd, J = 10.9, 3.0 Hz, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.77 (dd, J = 11.0, 8.2 Hz, 1 H), 3.12 (br s, 2 H), 2.84 (br s, 2 H). Anal. Calcd. for $C_{27}H_{29}ClN_4O_4.2HCl.0.5H_2O$: C, 54.9; H, 5.5; N, 9.5. Found: C, 55.1; H., 5.5; N, 9.1%.

Example D: Preparation of ancillary ligands

1,4,7,10-Tetraazacyclododecane-1,7-dipropanesulfonic acid tetrahydrochloride (32).

A solution of perhydro-3,6,9,12-tetraazacyclopenteno[1,3-*f*,*g*]acenaphthylene **(30)** (0.50 g, 2.58 mmol) [Weisman et al., Tetrahedron Lett., 21, 1980, 335] and 1,3-propanesultone (1.57 g, 12.9 mmol) in CH_3CN (20 mL) was stirred at 80 °C under N_2 for 72 h. The suspension was cooled to room temperature and the white precipitate was filtered and washed with excess CH_3CN to give 1,7-bis(3-sulfopropyl)-4,10-diaza-1,7-diazoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane **(31)** (0.98 g, 86%): mp 279-281 °C; ^{1}H NMR (D_2O) δ 4.49 (s, 2 H), 3.95 (m, 8 H),

3.82 (bd, J = 13.3, 2 H), 3.60 (m, 4 H), 3.38 (bd, J = 14.0, 2 H), 3.05 (m, 8 H), 2.39 (m, 2 H), 2.27 (m, 2 H); ^{13}C NMR (D_2O) δ 81.6, 64.2, 58.7, 57.6, 49.8, 49.0, 45.3, 21.4. $C_{16}H_{30}N_4O_6S_2$ requires M+H 439.1685. Found (FAB) 439.1686.

A mixture of **31** (0.50 g, 1.14 mmol) and hydrazine monohydrate (15 mL, 98%) were heated (100 °C) under N_2 for 48 h. Excess hydrazine was removed and the residue was dissolved in H_2O. Acidification with HCl gave a yellow solution. Evaporation of H_2O gave a brown solid (hygroscopic). Trituration with MeOH (x 10) gave **32** (0.59 g, 91%) as a cream powder: mp 322-325 °C; ^{1}H NMR (D_2O) δ 3.24 (m, 8 H), 2.94 (m, 12 H), 2.82 (m, 4 H), 1.95 (quintet, J = 7.4, 4 H); ^{13}C NMR (D_2O) δ 53.9, 51.7, 49.9, 45.1, 21.7.

1,4,7,10-Tetraazacyclododecane-1-butanesulfonic acid tetrahydrochloride (34).

A solution of **30** (0.50 g, 2.58 mmol) and 1,4-butanesultone (1.75 g, 12.9 mmol) in CH_3CN (15 mL) was stirred at 60 °C under N_2 for 48 h. The suspension was cooled to room temperature and the white precipitate was filtered and washed with excess CH_3CN to give 4-decahydro-4a,6a,8a-triaza-2a-azoniacyclopenta[*f*,*g*]acenaphthylen-2a-yl-1-butanesulfonate **(33)** (0.82 g, 96%): mp 301-303 °C; ^{1}H NMR (D_2O) δ 3.91 (m, 1 H), 3.91 (d, J = 2.5, 1 H), 3.80 (m 3 H), 3.67 (m, 1 H), 3.58 (d, J = 2.7, 1 H), 3.53 (m, 1 H), 3.43 (m, 1 H), 3.24 (m, 4 H), 3.00 (t, J = 7.3, 2 H), 2.87 (m, 5 H), 2.50 (m, 2 H), 2.09 (m, 1 H), 1.98 (m, 1 H), 1.85 (m, 2 H); ^{13}C NMR (D_2O) δ 86.5, 74.4, 64.8, 60.4, 59.6, 53.9, 52.5, 51.1, 50.9, 50.4, 50.3, 46.3, 24.2, 24.0. $C_{14}H_{26}N_2O_4S$ requires M+H 331.1804. Found (FAB) 331.1806.

A mixture of **33** (0.30 g, 0.92 mmol) and hydrazine monohydrate (6 mL, 98%) was heated (80 °C) under N_2 for 36 h. Excess hydrazine was removed and the residue was dissolved in H_2O. Acidification with HCl gave a yellow solution. Evaporation of H_2O gave a brown solid (hygroscopic). Trituration with MeOH (x 10) gave **34** (0.41 g, 97%) as a cream powder: mp 322-325 °C; ^{1}H NMR (D_2O) δ

3.20 (m, 16 H), 2.95 (m, 4 H), 1.78 (m, 4 H); ^{13}C NMR (D_2O) δ 56.2, 52.9, 52.1, 51.6, 46.4, 45.5, 44.9, 25.1, 24.4.

1,4,7,10-Tetraazacyclododecane-1,7-dipentanoic acid (36).
A solution of **30** (0.10 g, 0.52 mmol) and ethyl 4-iodobutyrate (0.79 g, 3.09 mmol) [Nudelman et al., Bioorg. Chem., 26, 1998, 157] in CH_3CN (5 mL) was stirred at 60 °C under N_2 for 6 days. A further portion of the iodide (0.26 g, 1.03 mmol) was added and the reaction was stirred at 60 °C under N_2 for 3 weeks. CH_3CN was removed and the residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (x 6). H_2O was evaporated and the residue was solidified with CH_3CN/Et_2O followed by trituration with Et_2O (x 4) to give 1,7-bis(ethoxycarbonylbutyl)-4,10-diaza-1,7-diazoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane diiodide (**35**) (0.32 g, 87%): ^{1}H NMR (D_2O) δ 4.46 (s, 2 H), 4.17 (q, J = 7.2, 4 H), 3.92 (m, 6 H), 3.77 (m, 4 H), 3.59 (m, 2 H), 3.45 (td, J = 12.8, 4.1, 2 H), 3.35 (bd, J = 13.9, 2 H), 3.06 (m, 4 H), 2.48 (t, J = 7.3, 4 H), 1.96 (m, 2 H), 1.85 (m, 2 H), 1.69 (quintet, J = 7.3, 4 H), 1.25 (t, J = 7.2, 6 H); ^{13}C NMR (D_2O) δ 178.6, 81.2, 64.5, 64.4, 60.2, 57.9, 49.0, 45.3, 35.9, 24.8, 23.8, 16.1. $C_{24}H_{44}I_2N_4O_4$ requires M+H-I 579.2407. Found (FAB) 579.2410.

A mixture of **35** (0.05 g, 0.08 mmol) and 15% aqueous KOH (5 mL) was stirred at 70 °C under N_2 for 48 h. Water was evaporated and the residue was acidified to pH 2.5 with HCl. The mixture was loaded onto a DOWEX 50W-X8 cation exchange resin (H^+ form). Elution with H_2O followed by 0.5M NH_3 gave **36** (0.03 g, 100%) as a colourless oil: ^{1}H NMR (D_2O) δ 2.86 (m, 8 H), 2.68 (m, 8H), 2.53 (t, J = 7.4, 4 H), 2.20 (q, J = 7.0, 4 H), 1.55 (m, 4 H), 1.47 (m, 4 H); ^{13}C NMR (D_2O) δ 183.1, 53.1, 49.1, 42.8, 37.1, 24.1, 23.8. $C_{18}H_{36}N_4O_4$ requires M+H 373.2815. Found (FAB) 373.2810.

Example E. Preparation of metal complexes.

Preparation of Complex M1 of Table 1. [[Co(cyclen)18a)](ClO_4)$_2$]. [Co(cyclen)(NO_2)$_2$](NO_2) (**38**) [Collman and Schneider, Inorg. Chem. 1966, 5, 1380] (1.03 g, 2.79 mmol) was cautiously added with stirring to neat triflic acid (10 mL) cooled in an ice bath. The solution was bubbled with N_2 to remove NO_x gas and warmed briefly at 40-50 °C until reaction was complete. Dry Et_2O (250 mL was added slowly to the above cold solution (ice-bath) with vigorous stirring, and the resulting precipitate was filtered off, washed (4 x dry Et_2O) and dried in a desiccator to give [Co(cyclen)(OTf)$_2$](OTf) (**39**) (1.95 g, 100%). Anal. Calcd. for $C_{11}H_{24}CoF_9N_4O_{11}S_3$: C, 18.49; H, 3.39; N, 7.85. Found: C, 18.43; H, 3.49; N, 7.84. HRMS FAB$^+$ [M-OTf]$^+$ calculated for: $C_{10}H_{20}CoF_6N_4O_6S_2$= 529.00605. Found: 529.00406. (**39**) (90 mg, 0.132 mmol) was dissolved in dry CH_3CN (3 mL) and **18a** (62 mg, 0.132 mmol) was added. To the stirred solution was added iPr$_2$NEt (25 mg, 1.5 equiv). This resulted in rapid darkening of the solution to a brown colour but with significant amounts of suspended yellow solid (unreacted/undissolved) **18a** present. The mixture was stirred at room temperature for 11 days, during which time nearly all of the suspended solid disappeared. The small amount remaining was removed by filtration through a 0.45 μ membrane filter and the filtrate made slightly acidic with dilute aqueous $HClO_4$. Excess 1 M $NaClO_4$ (aq) was added and the solution was extracted 4 x with 5 mL CH_3NO_2. The combined extracts were evaporated to dryness, the residue resuspended in dry Et_2O (15 mL) and again evaporated to dryness (first on a Rotovapor, finally on a vacuum line) below 20 °C, to give crude product as brown flakes of glassy material (103 mg, 86%). HRMS FAB [M-ClO$_4$]$^+$. This material was further purified on reverse-phase HPLC, and the pooled pure fractions were concentrated under reduced pressure, then combined with excess aqueous 1 M $NaClO_4$ and extracted 5 x with CH_2Cl_2. The combined organic extracts were treated as above to give complex **M1** as brownish flakes (~70 mg). HRMS FAB [M-2ClO$_4$-H]$^+$ Calcd for $C_{32}H_{41}{}^{35}ClCoN_7O_5$; 697.21897. Found, 697.21327. Calcd for $C_{32}H_{41}{}^{37}ClCoN_7O_5$; 699.21602. Found, 699.21601.

Preparation of Complex M2 of Table 1. [[Co(cyclen)(18c)](ClO_4)$_2$]

[Co(cyclen)(OTf)$_2$](OTf) (**39**) (0.087 g, 0.128 mmol) was dissolved in dry CH_3CN (4 mL) and **18c** (0.052 g, 0.115 mmol) was added. The mixture was stirred at room temperature for 8 h. then cooled overnight at 5 °C. A small amount of unreacted **18c** was removed by filtration and the bright yellow solid washed with cold CH_3CN and the washes added to the filtrate. This dark brown solution was reduced to ca. 2 mL by evaporation of solvent under reduced pressure at room temperature and then chromatographed on a short (3.3 x 40 mm) flash silica gel column (0.32-0.60 µm). Elution started with MeOH/CH_3NO_2 (5 %) which was stepwise enriched with MeOH up to 15 %. At this concentration the main band was eluted first followed closely by a small yellow brown band. A stationary red band remains at the top of the column. Removal of the solvent on a rotary evaporator then on a vacuum line to give **M2** as a brown glassy residue (0.089 g, 79 %). HRMS FAB$^+$ [M-2OTf]$^+$ Calcd. for $C_{33}H_{45}{}^{35}ClCoN_7O_3$ 681.26044. Found, 681.26064; for ^{37}Cl = 683.25749. Found, 683.26086.

Preparation of Complex M3 of Table 1. [[Co(cyclen)(18b)](ClO$_4$)$_2$]

This was prepared as above from **39** (0.101 g, 0.149 mmol) and **18b** (0.055 g, 0.118 mmol) to give, after flash chromatography on silica gel, **M3** (0.078 g, 67 %). HRMS FAB$^+$ [M-2OTf]$^+$ calculated for $C_{33}H_{44}{}^{35}ClCoN_8O_3$ 694.25569. Found = 694.25305; for ^{37}Cl = 696.25274. Found = 696.25401.

Preparation of Complex M4 of Table 1. [Cr(acac)$_2$(18a)].

Solid **18a** (20 mg, 0.0427 mmol) was added to a solution of [Cr(acac)$_2$(H$_2$O)$_2$]ClO$_4$·2H$_2$O (mixture of *cis* and *trans* isomers; Ogino, et al., Inorg. Chem. 1988, *27*, 986) (0.03 g, 0.071 mmol) in dry CH_3CN (3 mL). The mixture was stirred and a solution of iPr$_2$NEt (6 mg, 0.0464 mmol) in CH_3CN (0.5 mL) was added gradually over 1 h. The solution was warmed in an oil bath at 50 °C for 0.5 h, then stirred at ambient temperature for 2 weeks. During this period undissolved **18a** gradually disappeared as the complexation reaction proceeded giving a clear red-brown solution. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (1.0 mL) and purified by flash

chromatography on silica gel. Elution with a $CH_3CN/CHCl_3$ gradient from 0 to 50% CH_3CN eluted a single yellow-brown band that trailed somewhat near the bottom of the column. The trailing material was eluted separately with 100% CH_3CN. A small amount of green irreversibly absorbed material was left at the top. The main band and tailing fraction were evaporated to dryness under reduced pressure to give yellow-brown powders of $Cr(acac)_2$(**18a**) (18 mg, 59%) and (5 mg, 16%), respectively.

These two samples gave identical accurate mass spectral results; approximately equal amounts of both $[M]^+$ and $[M + H]^+$ ions observed with relative intensities consistent with one ^{35}Cl or ^{37}Cl per molecule. FAB$^+$-MS: $[M]^+$ calc. for $C_{34}H_{35}{}^{35}Cl^{52}CrN_3O_9$ = 716.14669. Found, $[M]^+$ = 716.14642. $[M + H]^+$ calc. for $C_{34}H_{36}{}^{37}Cl^{52}CrN_3O_9$ = 719.15157. Found, $[M + H]^+$ = 719.15122. Fragments corresponding to loss of acac ligand are observed, and the base peak corresponds to $Cr(acac)_2$. Analytical HPLC on an RP C-18 column using gradient elution starting from a 1:1 (v/v) mixture of 80% aqueous CH_3CN and phosphate buffer (pH = 7.4, 0.04 M) showed one major peak (96.7%) with a prominent UV absorption band at 339 nm. A small amount (0.45%) of uncomplexed **2** could be detected and its identity was confirmed by spiking. Because of the paramagnetic properties of the Cr(III) present in this complex, ^1H or ^{13}C resonances were not observed by NMR.

Preparation of Complex M5 of Table 1. [Co(Me$_2$dtc)$_2$(18a)]

$[Co_2(Me_2dtc)_5]BF_4$ (105 mg, 0.1303 mmol) [Hendrickson et al., J. Chem. Soc. Dalton Trans. 1975, 2182] was added to a suspension of **18a** (46 mg, 0.0983 mmol) in 5% $MeOH/CH_2Cl_2$ (4 mL). iPr_2NEt (25 mg, 2 equiv) was added to stirred suspension in two portions with the second added one day after the first. Stirring was continued at room temperature for 8 days, by which time very little suspended/unreacted **18a** was evident, and the colour of the solution was the deep green of the co-product $Co(Me_2dtc)_3$. The solution was filtered and the filtrate evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (2 mL)

and chromatographed on a flash silica gel column. Elution began in CH_2Cl_2, and a large green band of $Co(Me_2dtc)_3$ was eluted. Stepwise enrichment with CH_3CN in increments of 10% was carried out until the product -[Co(Me_2dtc)$_2$(**18a**)] (**M5**) was eluted (with ca 50% CH_3CN/CH_2Cl_2). The main muddy yellow-green band was collected, and solvent was removed under reduced pressure to give the product as a brownish-green amorphous residue (48 mg, 63%). Analytical reverse-phase HPLC indicated no detectable free cytotoxic ligand **18a** present.

Preparation of Complex M6 of Table 1. [[Cr(acac)$_2$(29)]ClO_4)]

A suspension of **29** (31 mg, 0.058 mmol) in CH_3OH (0.5 mL) was treated with a solution of NaOH (5 mg, 0.119 mmol) dissolved in CH_3OH (0.5 mL), and the neutralised solution was immediately added to a another containing a mixture of *cis*- and *trans*-[Cr(acac)$_2$(OH_2)$_2$]ClO_4·$2H_2O$ (29 mg, 0.069 mmol) dissolved in CH_3CN (1.0 mL). The combined mixture was stirred at 50 °C for 15 min, cooled to room temperature and the solvent removed under reduced pressure. Chromatography on silica gel gave [Cr(acac)$_2$(**29**)]ClO_4 (**M6**) as a purple residue after drying under vacuum over silica gel desiccant. HRMS (FAB^+/NBA): Calculated [M^+] for $C_{37}H_{43}N_4{}^{35}ClCrO_8$, 758.21834. Found, 758.21745.

Preparation of Complex M7 of Table 1 [[Co(TACN)(8-HQ)(CN)]ClO_4]

Co(TACN)(NO_2)$_3$ was prepared from $Na_3[Co(NO_2)_6]$, using the method of Wieghardt et al., Chem. Ber., 1979, 112, 2220-2230. This was then used to prepare [Co(TACN)(H_2O)$_3$](OTf)$_3$ (91% yield), essentially by the method of Galsboel et al., Acta Chem. Scand., 1996, 50, 567-570. [Co(TACN)(H_2O)$_3$](OTf)$_3$ (360 mg, 0.509 mmol) was dissolved in EtOH (9 mL) and 8-hydroxyquinoline (8-HQ) (73 mg, 0.6 mmol) added as a solid. Immediately a solution of Et_3N (62 mg) in EtOH (~4 mL) was added to the stirred solution, which was then warmed briefly to complete the coordination of 8-HQ to the cobalt centre. NaCN (150 mg, 4 equiv) was added portionwise, and the mixture was stirred for 24 hours. During the addition of NaCN and occasionally thereafter, the pH was adjusted to ca. 7 by

addition of 0.1 M $HClO_4$. The red crystals and orange precipitate that formed were dissolved by dilution of the mixture with H_2O and the whole was loaded onto a Sephadex SP C-25 cation exchange column and thoroughly washed with H_2O. Elution with 0.05 M then 0.1 M $NaClO_4$ eluted the major band, and concentration of the eluate by evaporation under reduced pressure produced red-brown crystals of [Co(TACN)(8-HQ)(CN)]ClO_4 (**M7**) (117 mg, 51%) which were collected and washed with a little ice cold H_2O then 3 x with Et_2O. Anal. Calcd for $C_{16}H_{21}N_5ClO_5Co$: C, 41.98; H, 4.62; N, 15.30; Cl, 7.74. Found; C, 41.99; H, 4.44; N, 15.28; Cl, 7.93.

Biological activity

Selected complexes of Table 1, together with the uncomplexed cytotoxic ligands, were evaluated for cytotoxicity (measured as IC_{50} values in μM following a 4 h aerobic drug exposure) in a panel of mammalian cell lines, and the results are given in Table 2. AA8 is a Chinese hamster ovary line, and the UV4 cell line is a repair-defective ERCC-1 mutant, sensitive to agents whose cytotoxicity is due to bulky DNA adducts. EMT6 is a murine mammary carcinoma line, and SKOV3 is a human ovarian cancer line.

Table 2. Shows the results of the biological activity for various cytotoxins and their metal complexes. IC_{50} values are mean ± sem (number of experiments in parentheses) for exposure of the indicated cell lines to compounds for 4 hr under aerobic conditions.

Table 2

Compound	IC_{50} (μM)			
	AA8	UV4	EMT6	SKOV3
Cytotoxic ligands				
29	0.0058 ± 0.0007 (2)	0.0041 ± 0.0003 (2)	0.0028 0.0004 (2)	0.0062
18a	0.00014 ± 0.000022 (7)	0.00007 ± 0.000015 (6)	0.000051 ± 0.000008 (5)	0.00025 ± 0.000037 (8)
27	0.0079 ± 0.002 (4)	0.0029 ± 0.006 (4)	0.0026 ± 0.0005 (4)	0.012 ± 0.0023 (4)
8-HQ	2.07 ± 0.02 (3)	2.16 ± 0.12(3)	3.92 ± 1.04(2)	4.07 ± 0.89(2)
Ancillary ligands				
TACN (**VIIIc**: R^1-R^3=H)	12700 ± 5770 (2)	10100 ± 3930 (2)	7710 ± 1010 (2)	13500 ± 5480 (2)
Cyclen (**IX**; Z^1-Z^4=$(CH_2)_2$; $R^{1\prime}$-$R^{4\prime}$=H)	13300 ± 2670 (2)	13800 ± 2180 (2)	9710 ± 2710 (3)	11500 ± 4410 (2)
Metal complexes				
M1	0.0152 ± 0.0006 (2)	0.0051 ± 0.0002 (2)	0.0133 ± 0.0008 (2)	0.015 ± 0.005 (3)
M4	0.088 ± 0.017 (3)	0.03 ± 0.0018 (3)	0.039 ± 0.011 (3)	0.11 ± 0.018(3)
M5	0.028 ± 0.003 (3)	0.015 ± 0.001 (3)	0.0095 ± 0.0012 (2)	0.016 ± 0.003 (3)
M7	5,670 ± 45.0 (2)	6,140 ± 820 (2)	3,580 ± 95.4 (2)	6,380 ± 1750 (3)

The results of Table 2 show that the cytotoxic ligands 29, 18a and 27 are exceptionally cytotoxic. The results of Table 2 also show that metal complexation

results in considerable abrogation of cytotoxicity, indicating the utility of this approach in forming less toxic prodrugs of these compounds.

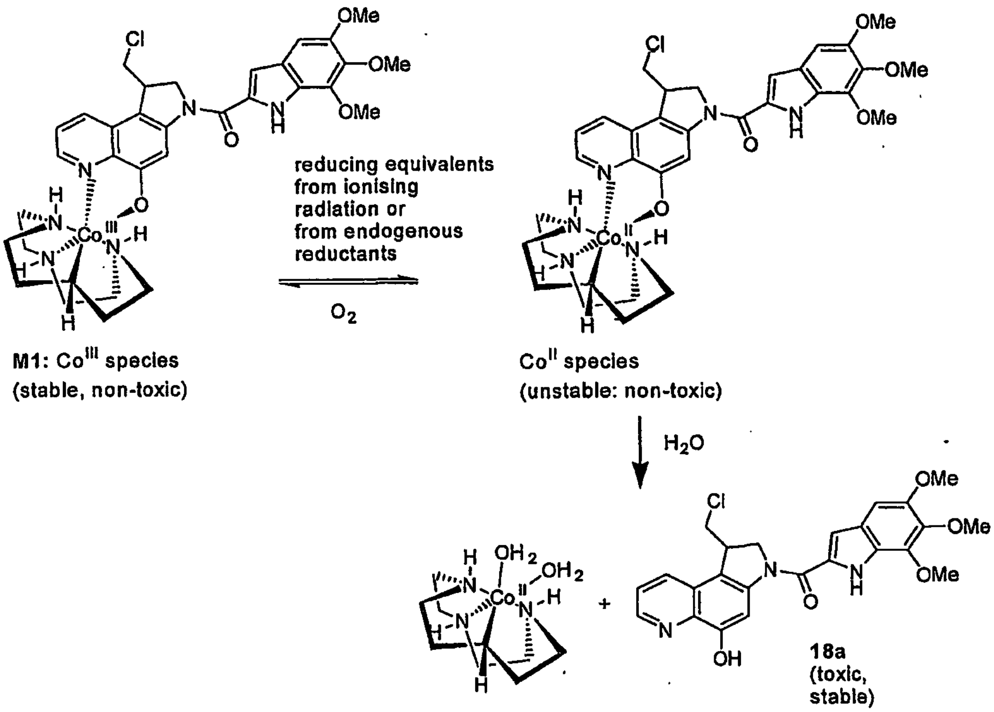
Complex M1 listed in Table 1 was also evaluated for its ability to release the cytotoxic ligands when exposed to ionising radiation in deoxygenated sodium formate buffer (measured as G values in μM/Gy for radiolytic reduction, where the G value for total reductants is 0.68 μM/Gy), and the results are given in Table 3.

Table 3. G values (μM/Gy) for release of cytotoxic ligand on radiolytic reduction in deoxygenated sodium formate buffer using 15 μM prodrug (complex **M1**).

No	Metal	Cytotoxic ligand	Ancillary ligands	G value (μmol/Gy)
M1	Co	**18a**	Cyclen	0.75

The results of Table 3 show that certain of these metal complexes also have the potential to cleanly release their cytotoxic ligand in good yield following exposure to ionising radiation. As a specific example, Figure 1 shows the release of cytotoxin **18a** (SN 26800) from complex **M1** (SN 27892) when irradiated in 0.1M sodium formate buffer pH 7.0 under hypoxic conditions.

It is thought that the mechanism of activation of the prodrug is as illustrated in the following mechanistic pathway.



The metal complexes also show an ability to be activated by endogenous enzymes under hypoxia, as shown for metal complex **M1** in Table 4 and Figure 2. Table 4 and Figure 2 also show that the corresponding cytotoxic ligand **18a** is not activated by endogenous enzymes under hypoxic conditions. Thus the metal complexes have utility as hypoxia- as well as radiation-activated cytotoxins.

TABLE 4: Activation of metal complex **M1** (but not the cytotoxin **18a**) under hypoxia (4 h exposure).

IC$_{50}$ (nM)

	A549wt/s			**SKOV3**			**WiDr-2**		
	oxic	anoxic	HCR	oxic	anoxic	HCR	oxic	anoxic	HCR
18a	0.050 ± 0.016(3)	0.050 ± 0.014(2)	0.79 ± 0.35 (2)	0.25 ± 0.037(8)	0.35 ± 0.093(2)	0.61(1)	-	-	
M1	5.60 ± 0.00(2)	0.38± 0.16(2)	18.0 ± 7.7(2)	15.0 ± 5.0(3)	1.7 ± 0.97(2)	8.1(1)	6.6 ± 0.45(2)	1.7 ± 0.10(2)	3.90 ± 0.50(2)

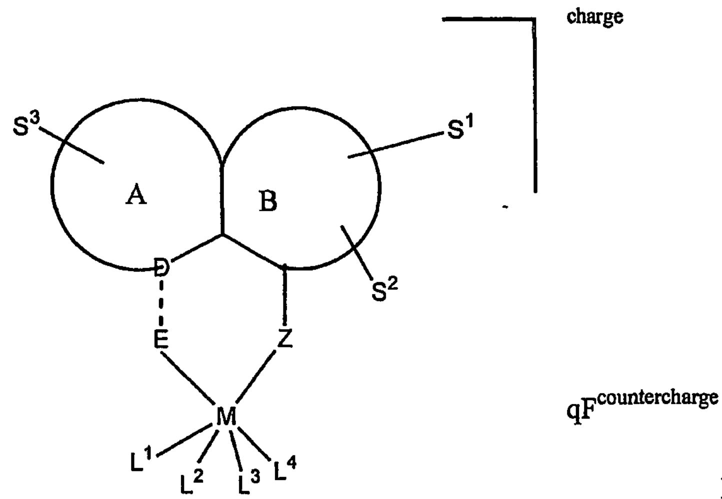
In Table 4, A549wt/s is a wild-type human colon carcinoma cell line, SKOV3 is a human ovarian cancer cell line and WiDr-2 is a clonal cell line derived from the WiDr human colon carcinoma line. IC_{50}s (in μM) are determined under both oxic and hypoxic conditions, and the hypoxic cytotoxicity ratio (HCR) is the average intra-experiment ratio of the IC_{50}s measured under oxic and hypoxic conditions.

Wherein the foregoing description reference has been made to reagents, or integers having known equivalents thereof, then those equivalents are herein incorporated as if individually set forth.

While this invention has been described with reference to certain embodiments and examples, it is to be appreciated that further modifications and variations may be made to embodiments and examples without departing from the spirit or scope of the invention.

<u>What we claim is:</u>

1 A metal complex represented by Formula I



I

wherein:

A is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

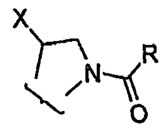
D is selected from C or N;

E is selected from a direct bond, OH or NR^1_2, where each R^1 independently represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, when D represents C; or

M is selected from Co^{III}, Co^{II}, Cr^{III} or Cr^{II};

Z is selected from O, NR^2, where R^2 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups,

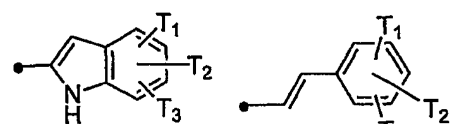
S^1 and S^2 together represent formula V



V

wherein X is selected from a group including halogen, CH_2-halogen, CH_2OCO-(C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups), CH_2-phosphate group or $CH_2OSO_2R^3$, where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**



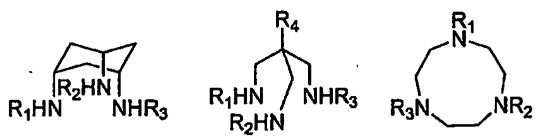
VI VII ,

wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, $NR^5{}_2$ or $NHCOR^5$, where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or $O(CH_2)_nNR^6{}_2$, where each n is independently 1, 2, 3 or 4 and each R^6 is independently selected from H or a

C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and • represents the point of attachment of R to Formula V defined above, and S^3 is selected from H, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, $CO_2[(C_{1-6}alkyl)$ wherein said alkyl is optionally substituted with amino, or hydroxy groups]; OR^7, $NR^7{}_2$, or $CONHR^7$, where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 5 or 6 membered cyclic system optionally containing one or more heteroatoms fused to ring system A

defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen groups, and

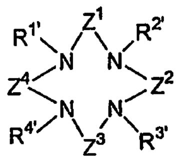
wherein ligands L^1-L^4 are each independently selected in combinations from anionic monodentate ligands, including CN^-, SCN^-, halide, NO_2^-; bidentate ligands including MeCOCHJCOMe (Jacac; deprotonated in the complex), where J = H, Me, Cl, SMe, SO_2Me, $S(CH_2)_nSO_3H$, $S(CH_2)_nCO_2H$, $S(CH_2)_nOP(O)(OH)_2$, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$, $CH_2(CH_2)_nOP(O)(OH)_2$, $S(CH_2)_nP(O)(OH)_2$ or $CH_2(CH_2)_nP(O)(OH)_2$, where n is from 1-4;or tridentate ligands **VIIIa-VIIIc** (= respectively TACH, TAME and TACN when R_1-R_3=H).



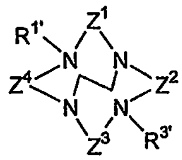
VIIIa VIIIb VIIIc

wherein each R_1-R_4 are independently selected from H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nP(O)(OH)$ or $CH_2(CH_2)_nNR^8_2$, where each n is independently 1, 2, 3 or 4 and each R^8 independently represents H, or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or

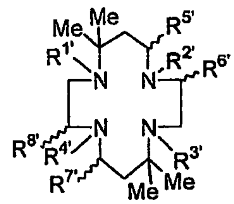
L^1-L^4 can also be selected from any one of the tetradentate ligands **IX-XVII**, or any two of the bidentate ligands **XVIII**, or any combination of the bidentate ligands **XVIII** together with any of the monodentate ligands L^1-L^4 defined above;



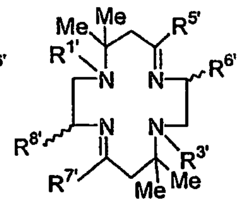
IX



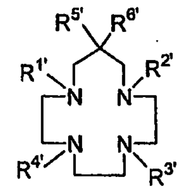
X



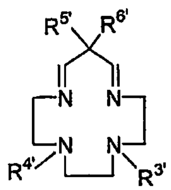
XI



XII



XIII



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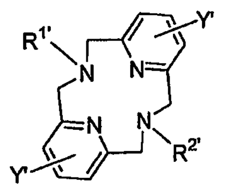
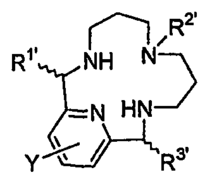
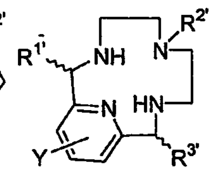


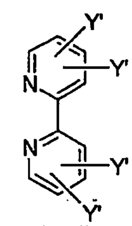
XV



XVI



XVII



XVIII

wherein in formulae **IX-XVIII**, $R^{1'}$ to $R^{8'}$ each independently represent H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nOP(O)(OH)_2$ or $CH_2(CH_2)_nNMe_2$, where each n is independently 1, 2, 3 or 4;

each Z^1-Z^4 is independently selected from $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2OCH_2-$ or $-CH_2N(R^9)CH_2-$; where R^9 represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and

each Y' is independently selected from H, halogen, SO_2Me, $O(C_1-C_6alkyl)$, NR^{10}_2, where each R^{10} is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $Q^1(CH_2)_nQ^2$, wherein Q^1 is selected from –O-, $-CH_2-$, -NH-, -CONH-, $-CO_2-$ or $-SO_2-$, and Q^2 is selected from $-CO_2H$, $-SO_3H$, $-OP(O)(OH)_2$ or $-NR^{11}_2$ where each R^{11} is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

wherein the overall charge on the complex is neutral, positive or negative and wherein in the case of a non-neutral complex $F^{countercharge}$ is selected from a range of physiologically acceptable-counterions, including halide$^-$, NO_3^-, NH_4^+ or Na^+; and

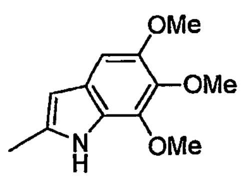
wherein q is the required number to neutralise the overall charge on the complex; and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof.

2 The metal complex according to claim 1 wherein the rings A and B of Formula I as defined in claim 1 together represent an 8-substituted quinoline system.

3 The metal complex according to any claim 1 or claim 2 wherein Z represents –O-.

4 The metal complex according to any claims 1 or 3 wherein Z represents -NH-.

5 The metal complex according to any one of claims 1 to 4 wherein R is selected from one of



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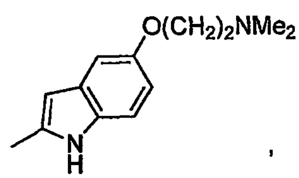

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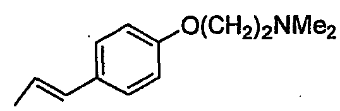

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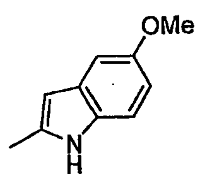

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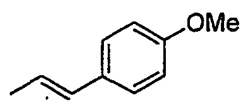

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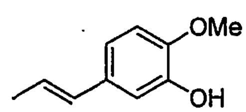

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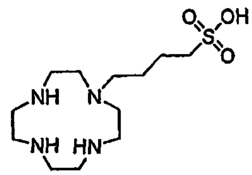
6 The metal complex according to any one of claims 1 to 5 wherein one of the ligands L^1-L^4 is selected from the following



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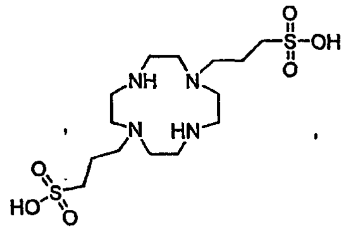

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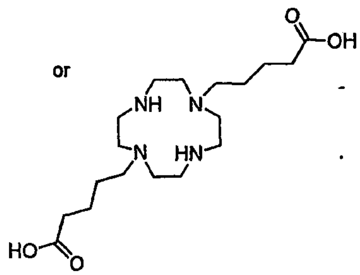

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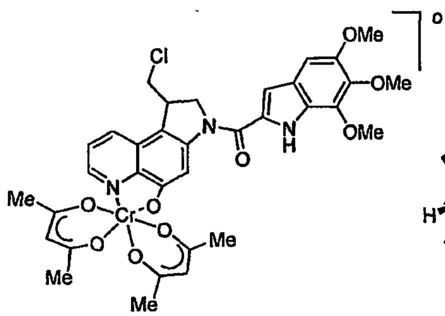
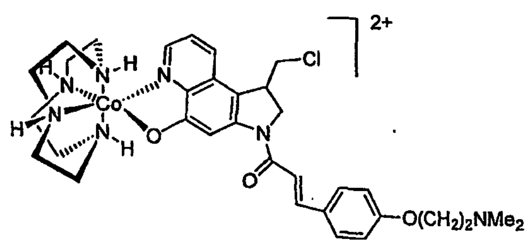
7 The metal complex according to any one of claims 1 to 6 wherein X is CH_2Cl.

8 The metal complex according to any one of claims 1 to 7 selected from one of the following;





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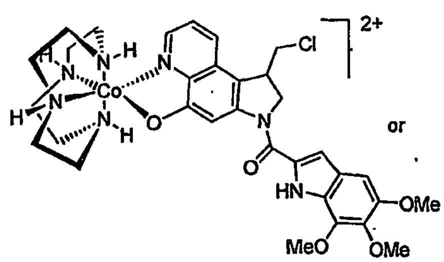

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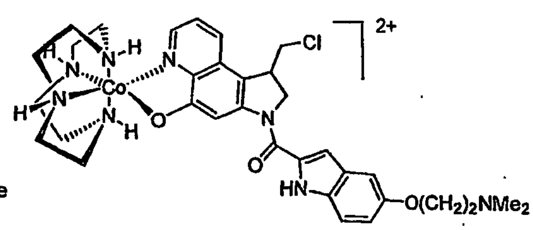

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9 A method of providing cancer treatment, which includes the steps of

(a) administering to a patient in need of such therapy an effective amount of a metal complex of Formula I as defined in any one of claims 1 to 8, and

(a) activating the metal complex of Formula I under hypoxic conditions via reduction, either enzymatically or by a non-enzymatic endogenous reducing agents, or by ionizing radiation,

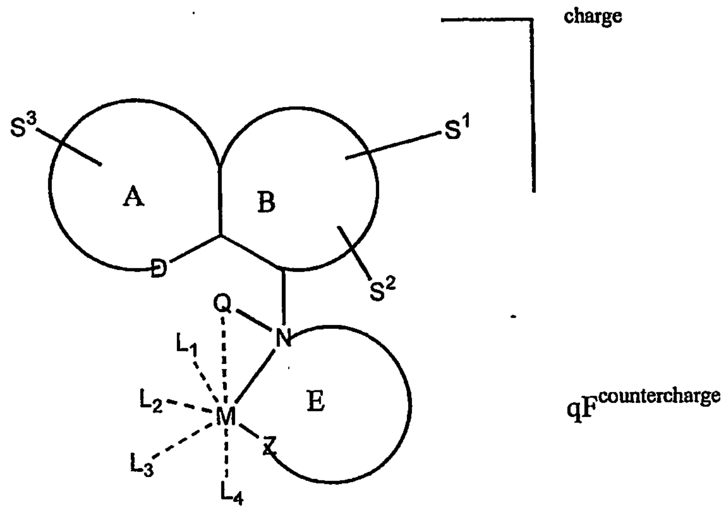
wherein said activation releases a sufficient amount of an effector from said metal complex of Formula I.

10 The method according to claim 9 including the alternative step of activation of the metal complex of Formula I as defined in any one of claims 1 to 8 by radiotherapy radiation.

11 A composition comprising as an active agent a metal complex of Formula I as defined in any one of claims 1 to 8 and a pharmaceutically acceptable excipient, adjuvant or carrier.

12 The use, in the manufacture of a medicament, of an effective amount of a metal complex of Formula I as defined in any one of claims 1 to 8 for use in treating a subject in need of cancer treatment.

13 A metal complex represented by Formula **Ia**



Ia

wherein:

A is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

D is selected from C or N;

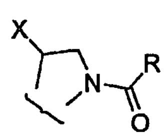
E is selected from a 5 or 6 membered ring system optionally containing one or more heteroatoms and optionally substituted with one or more $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halogen, hydroxy, phosphate, cyano or amino groups

M is selected from Co^{III}, Co^{II}, Cr^{III} or Cr^{II};

Z represents NH_2 or NHMe,

Q represents H, $C_{1\text{-}6}$alkyl, or $(CH_2)_2NH_2$, when Q represents $(CH_2)_2NH_2$, Q will become a ligand for M and replace one of ligands L^1-L^4 defined below,

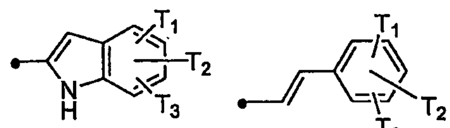
S^1 and S^2 together represent formula **V**



V

wherein X is selected from a group including halogen, CH_2-halogen, CH_2CN, CH_2CO_2-(C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups), CH_2-phosphate group, $CH_2OSO_2R^3$ or OSO_2R^3 where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**



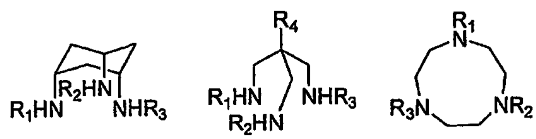
VI VII ,

wherein each T_1, T_2 and T_3 is indepeñdently selected from H, $OPO(OH)_2$, OR^2, $NR^2{}_2$ where each R^2 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^3{}_2$, where each n is independently 1, 2, 3 or 4, and each R^3 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and

• represents the point of attachment of R to Formula V defined above, and

S^3 is selected from H, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, $CO_2(C_{1-6}$alkyl) wherein said alkyl is optionally substituted with amino, or halogen groups, OR^4, $NR^4{}_2$, $CONHR^4$, where each R^4 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen groups, and

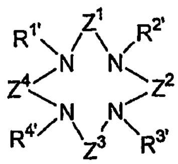
wherein ligands L^1-L^4 are each independently selected in combinations from anionic monodentate ligands, including CN^-, SCN^-, halide, NO_3^-; bidentate ligands including MeCOCHJCOMe (Jacac; deprotonated in the complex), where J = H, Me, Cl, SMe, SO_2Me, $S(CH_2)_nSO_3H$, $S(CH_2)_nCO_2H$, $S(CH_2)_nOP(O)(OH)_2$, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$, $CH_2(CH_2)_nOP(O)(OH)_2$, $S(CH_2)_nP(O)(OH)_2$ $CH_2(CH_2)_nP(O)(OH)_2$, or where each n is independently 1, 2, 3 or 4; or tridentate ligands **VIIIa-VIIIc** (=respectively TACH, TAME and TACN when R_1-R_3=H),

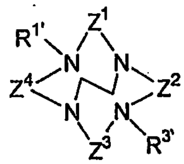


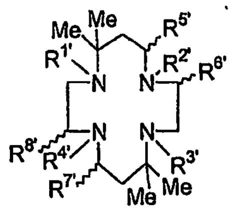
VIIIa VIIIb VIIIc

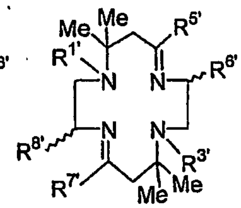
wherein R_1-R_4 are each independently selected from H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nOP(O)(OH)_2$ $CH_2(CH_2)_nP(O)(OH)_2$ or $CH_2(CH_2)_nNR^5{}_2$, where each n is independently 1, 2, 3 or 4 and each R^5 independently represents H, or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or

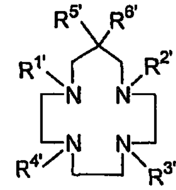
L^1-L^4 can also be selected from any one of the tetradentate ligands **IX-XVII**, or any two of the bidentate ligands **XVIII**, or any combination of the bidentate ligands **XVIII** together with any of the monodentate ligands L^1-L^4 defined above;

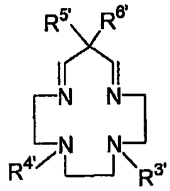

IX

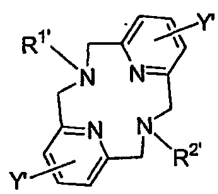

X

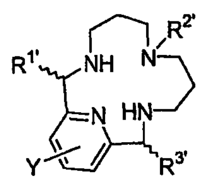

XI

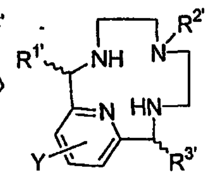

XII

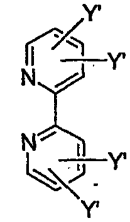

XIII


XIV


XV


XVI


XVII


XVIII

wherein in formulae **IX-XVIII**, $R^{1'}$ to $R^{8'}$ each independently represent H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nOP(O)(OH)_2$ or $CH_2(CH_2)_nNMe_2$, where each n is independently 1, 2, 3 or 4;
each Z^1-Z^4 is independently selected from -$(CH_2)_2$-, -$(CH_2)_3$-, -CH_2OCH_2- or -$CH_2N(R^6)CH_2$-; where R^6 represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and
each Y' is independently selected from H, halogen, SO_2Me, $O(C_1$-C_6alkyl), NR^7_2, where each R^7 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $Q^1(CH_2)_nQ^2$, wherein Q^1 is selected from –O-, -CH_2-, -NH-, -CONH-, -CO_2- or -SO_2-, and Q^2 is selected from -CO_2H, -SO_3H, -$OP(O)(OH)_2$ or –NR^8_2 where each R^8 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and
wherein the overall charge on the complex is neutral, positive or negative and wherein in the case of a non-neutral complex $F^{countercharge}$ is selected from a range of physiologically acceptable-counterions, including halide$^-$, NO_3^-, NH_4^+ or Na^+; and

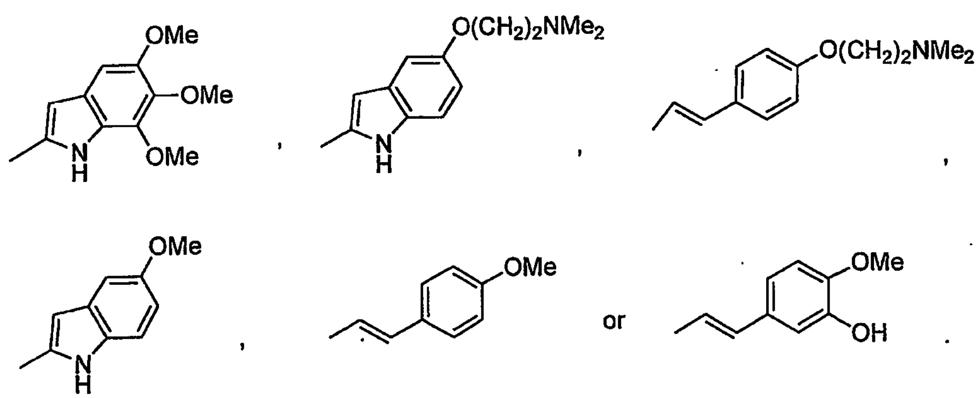
wherein q is the required number to neutralise the overall charge on the complex; and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof.

14 The metal complex according to claim 13 wherein rings A and B together represent an 8-substituted quinoline system.

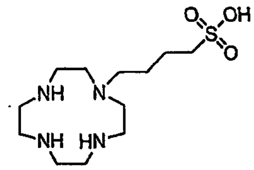
15 The metal complex according to claim 13 or claim 14 wherein Z represents -OH.

16 The metal complex according to claim 13 or claim 14 wherein Z represents -NH.

17 The metal complex according to any one of claims 13 to 16 wherein R is selected from one of



18 The metal complex according to any one of claims 13 to 17 wherein one of the ligands L^1-L^4 is selected from the following



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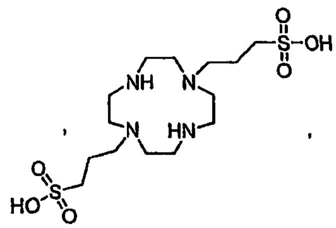

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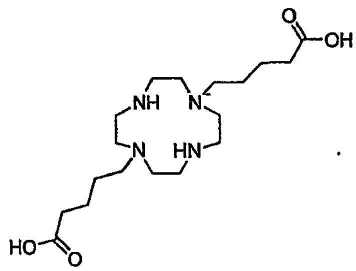

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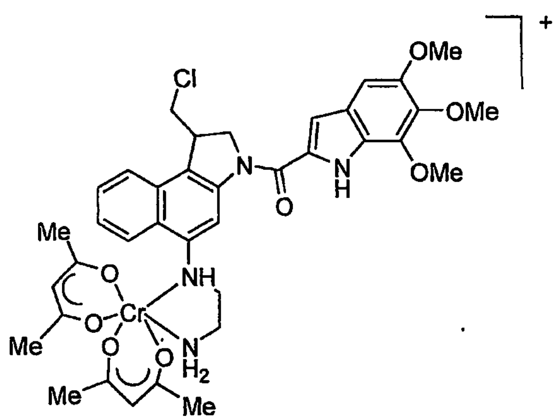
19 The metal complex according to any one of claims 13 to 18 wherein X is CH_2Cl.

20 The metal complex according to any one of claims 13 to 17 and 19 which represents



21 A method of providing cancer treatment, which includes the steps of

(a) administering to a patient in need of such therapy an effective amount of a metal complex of Formula Ia as defined in any one of claims 13 to 20, and

(b) activating the compound of Formula Ia under hypoxic conditions via reduction, either enzymatically or by non-enzymatic endogenous reducing agents, or by ionising radiation,

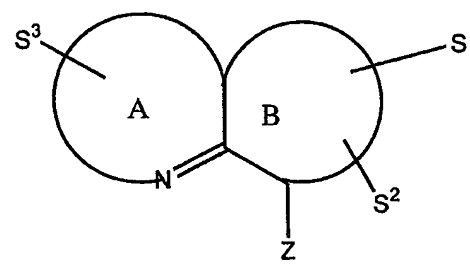
wherein said activation releases a sufficient amount of an effector, from said effective amount of the compound of Formula Ia.

22 The method according to claim 21 including the alternative step of activation of the metal complex of Formula **Ia** as defined in any one of claims 13 to 20 by radiotherapy radiation.

23 A composition comprising as an active agent a metal complex of Formula Ia as defined in any one of claims 13 to 20 and a pharmaceutically acceptable excipient, adjuvant or carrier.

24 The use, in the manufacture of a medicament, of an effective amount of a compound of Formula Ia as defined in any one of claims 13 to 20 for use in treating a subject in need of cancer treatment.

25 A heterocyclic compound of Formula **XIX**.



XIX

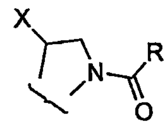
wherein

A is selected from a 5 or 6 membered ring system optionally containing one or more additional heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

Z is selected from OH or NR^1_2, where each R^1 independently represents H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;

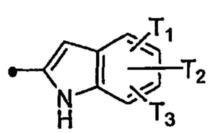
S^1 and S^2 together represent formula **V**



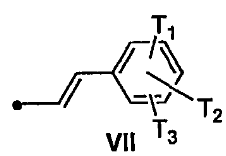
V

wherein X is selected from a leaving group including halogen, CH_2-halogen, CH_2CN, CH_2CO_2-(C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups), CH_2-phosphate group, $CH_2OSO_2R^3$ where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**



VI



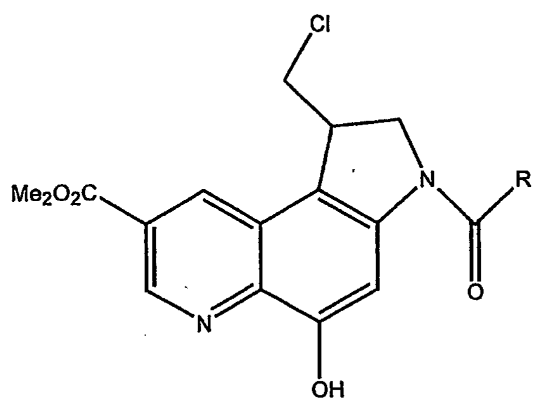
VII ,

wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, NR^5_2 where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^6_2$, where each n is independently 1, 2, 3 or 4 and each R^6 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups;

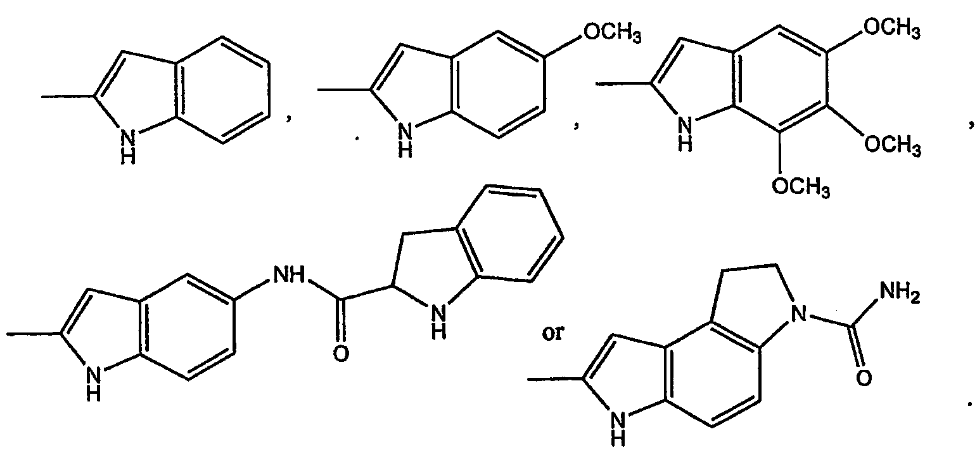
• represents the point of attachment to Formula **XIX** defined above;

S^3 is selected from H, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, $CO_2[(C_{1-6}$alkyl) wherein said alkyl is optionally substituted with amino, or

hydroxy groups], OR^7, NR^7_2, $CONHR^7$ where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen groups; and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof, with the proviso that when Z, A, B, X, S^1, S^2 and S^3 together represent



R does not represent one of the following

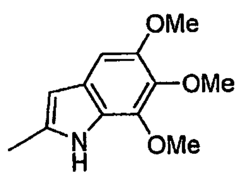


26 The heterocyclic compound according to claim 25 wherein the rings A and B together represent an 8-substituted quinoline system.

27 The heterocyclic compound according to claim 25 or claim 26 wherein Z represents -OH.

28 The heterocyclic compound according to any one of claims 25 to 27 wherein Z represents $-NH_2$.

29 The heterocyclic compound according to any one of claims 25 to 28 wherein R is selected from one of



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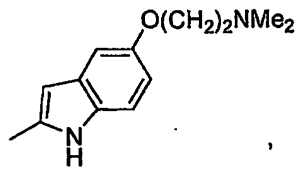

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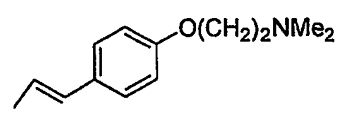

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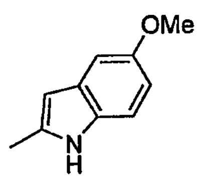

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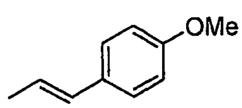

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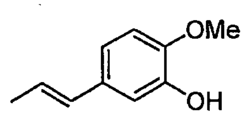

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30 The heterocyclic compound according to any one of claims 25 to 29 wherein X is $-CH_2Cl$.

31 The heterocyclic compound according to any one of claims 25 to 30 selected from one of the following

1-(chloromethyl)-5-hydroxy-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-3-({5-[2-(dimethylamino)ethoxy]-indol-2-yl}carbonyl)-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-3-((2*E*)-3-{4-[2-(dimethylamino)ethoxy]phenyl}-2-propenoyl)-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

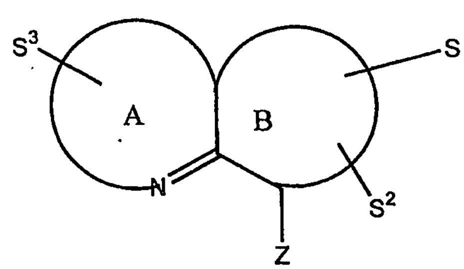
1-(chloromethyl)-5-hydroxy-3-[(5-methoxyindol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-3-[(2*E*)-3-(4-methoxyphenyl)-2-propenoyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-3-[(2*E*)-3-(3-hydroxy-4-methoxyphenyl)-2-propenoyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline and,

5-amino-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-*1H*-pyrrolo[3,2-*f*]quinoline.

32 A method of providing cancer treatment, which includes the step of administering to a patient in need of such therapy an effective amount of a heterocyclic compound of Formula **XIX**, as defined in any of claims 25-31.

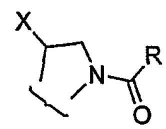


XIX

wherein

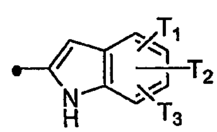
A is selected from a 5 or 6 membered ring system optionally containing one or more additional heteroatoms and optionally substituted with one or more

C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;
B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;
Z is selected from OH or $NR^1{}_2$, where each R^1 independently represents H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;
S^1 and S^2 together represent formula **V**

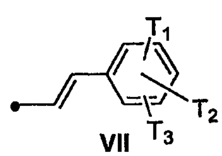


V

wherein X is selected from a leaving group including halogen, CH_2-halogen, CH_2CN, CH_2-phosphate group, $CH_2CO_2R^2$, where R^2 represents C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups; $CH_2OSO_2R^3$ where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydrogen or amino groups; and
R is selected from one of formulae **VI** or **VII**



VI



VII ,

wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, $NR^5{}_2$ where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^6{}_2$, where each n is independently 1, 2, 3 or 4 and each R^6 is independently selected from H or a C_{1-6} alkyl optionally substituted with one or more hydroxy or amino groups;
• represents the point of attachment to Formula **XIX** defined above;

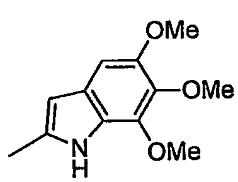
S^3 is selected from H, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, $CO_2[(C_{1}$-$_6$alkyl) wherein said alkyl is optionally substituted with amino or hydroxy groups], OR^7, $NR^7{}_2$, $CONHR^7$ where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen group; and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof.

33 The method according to claim 32 wherein the rings A and B of Formula **XIX** together represent an 8-substituted quinoline system.

34 The method according to claim 32 or claim 33 wherein Z of Formula XIX represents -OH.

35 The method according to any one of claims 32 to 34 wherein Z of Formula XIX represents $-NH_2$.

36 The method according to any one of claims 32 to 35 wherein R of Formula XIX is selected from one of



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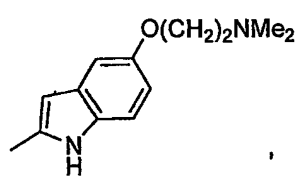

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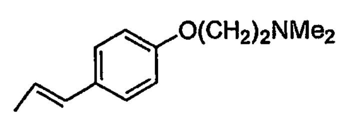

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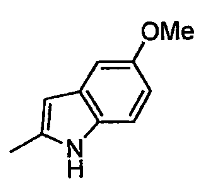

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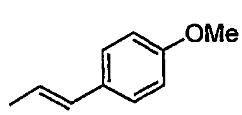

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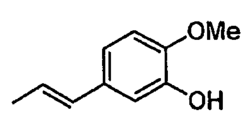

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37 The method according to any one of claims 32 to 36 wherein X of Formula XIX is $-CH_2Cl$.

38 The method according to any one of claims 32 to 37 wherein Formula XIX is selected from one of the following

1-(chloromethyl)-5-hydroxy-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-3-({5-[2-(dimethylamino)ethoxy]-indol-2-yl}carbonyl)-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-3-((2*E*)-3-{4-[2-(dimethylamino)ethoxy]phenyl}-2-propenoyl)-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

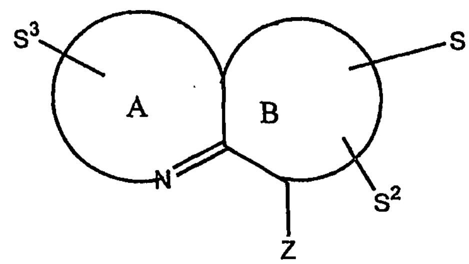
1-(chloromethyl)-5-hydroxy-3-[(5-methoxyindol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-3-[(2*E*)-3-(4-methoxyphenyl)-2-propenoyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-3-[(2*E*)-3-(3-hydroxy-4-methoxyphenyl)-2-propenoyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline and,

5-amino-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-*1H*-pyrrolo[3,2-*f*]quinoline.

39 A composition comprising as an active agent a compound of Formula **XIX**



XIX

wherein

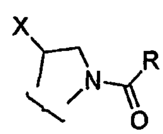
A is selected from a 5 or 6 membered ring system optionally containing one or more additional heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

Z is selected from OH or NR^1_2, where each R^1 independently represents H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;

Z is selected from O or NR^1, where R^1 represents H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;

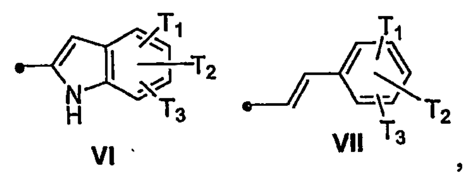
S^1 and S^2 together represent formula V



V

wherein X is selected from a leaving group including halogen, CH_2-halogen, CH_2CN, CH_2-phosphate group, $CH_2CO_2R^2$, where R^2 represents C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups; $CH_2OSO_2R^3$ where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^4$ where R^4 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**



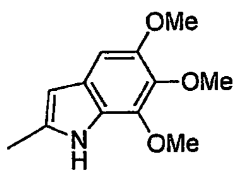
wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, $NR^5{}_2$ where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^6{}_2$, where each n is independently 1, 2, 3 or 4 and each R^6 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups;
• represents the point of attachment to Formula **XIX** defined above;
S^3 is selected from H, OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, $CO_2[(C_{1-6}$alkyl) wherein said alkyl is optionally substituted with amino, or hydroxy groups], OR^7, NR^7, $CONHR^7$ where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen groups; and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof and a pharmaceutically acceptable excipient, adjuvant or carrier.

40 The composition according to claim 39 wherein the rings A and B of Formula XIX together represent an 8-substituted quinoline system.

41 The composition according to claim 39 or claim 40 wherein Z of Formula XIX represents -OH.

42 The composition according to any one of claims 39 to 41 wherein Z of Formula XIX represents $-NH_2$.

43 The composition according to any one of claims 39 to 42 wherein R of Formula XIX is selected from one of



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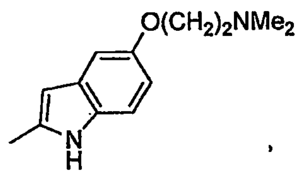

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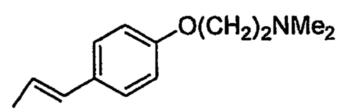

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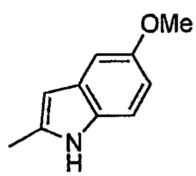

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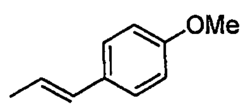

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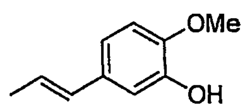

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44 The composition according to any one of claims 39 to 43 wherein X of Formula XIX is $-CH_2Cl$.

45 The composition according to any one of claims 39 to 44 wherein Formula XIX represents one of the following

1-(chloromethyl)-5-hydroxy-3-(5,6,7-trimethoxyindol-2-ylcarbonyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-3-({5-[2-(dimethylamino)ethoxy]-1*H*-indol-2-yl}carbonyl)-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-3-((2*E*)-3-{4-[2-(dimethylamino)ethoxy]phenyl}-2-propenoyl)-5-hydroxy-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

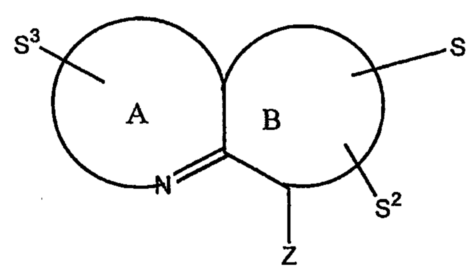
1-(chloromethyl)-5-hydroxy-3-[(5-methoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-3-[(2*E*)-3-(4-methoxyphenyl)-2-propenoyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-3-[(2*E*)-3-(3-hydroxy-4-methoxyphenyl)-2-propenoyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline, and

5-amino-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-*1H*-pyrrolo[3,2-*f*]quinoline.

46 The use, in the manufacture of a medicament, of an effective amount of a compound of Formula **XIX**



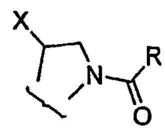
XIX

wherein

A is selected from a 5 or 6 membered ring system optionally containing one or more additional heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

B is selected from a 5 or 6 membered aromatic ring system optionally containing one or more heteroatoms and optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, halogen, hydroxy, phosphate, cyano or amino groups;

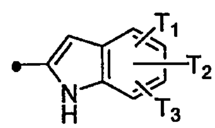
Z is selected from OH or NR^1_2, where each R^1 independently represents H or C_1-C_6alkyl optionally substituted with one or more amino, hydroxy, a halogen or cyano groups;



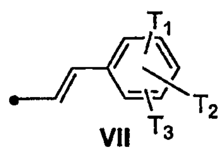
V

wherein X is selected from a leaving group including halogen, CH_2-halogen, CH_2CN, CH_2-phosphate group, $CH_2CO_2R^2$, whereR^2 represents C_1-C_6alkyl optionally substituted with one or more amino or hydroxy groups; $CH_2OSO_2R^3$ where R^3 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $CH_2OSO_2NHR^5$ where R^5 represents H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; and

R is selected from one of formulae **VI** or **VII**



VI



VII ,

wherein each T_1, T_2 and T_3 is independently selected from H, $OPO(OH)_2$, OR^5, $NR^5{}_2$ where each R^5 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or $O(CH_2)_nNR^6{}_2$, where each n is independently 1, 2, 3 or 4, and each R^6 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups;

• represents the point of attachment to Formula **XIX** defined above;

S^3 is selected from H, OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, $CO_2[(C_{1-6}$alkyl) wherein said alkyl is optionally substituted with amino, or hydroxy groups], OR^7, NR^7, $CONHR^7$ where each R^7 independently represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups; or S^3 represents an optionally substituted 4-8 membered cyclic system optionally

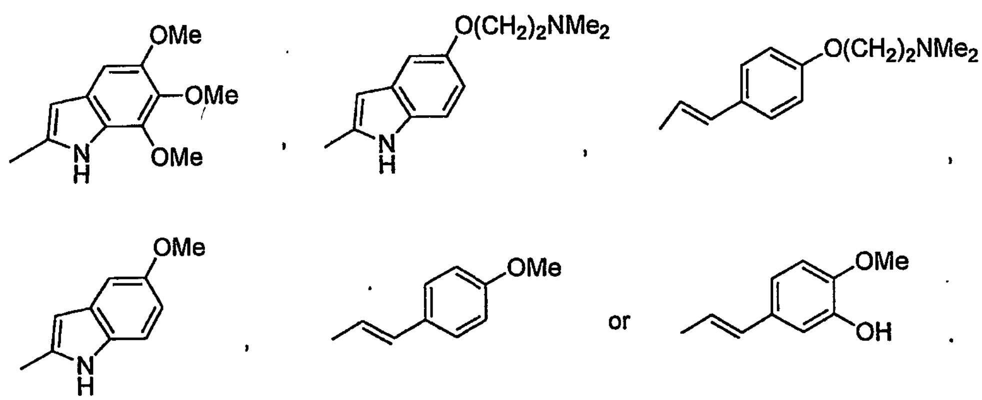
containing one or more hetoeroatoms fused to ring system A defined above, wherein said substituents are selected from OH, cyano, phosphate, amino, C_{1-6}alkyl, C_{1-6}alkoxy, and halogen groups, and including any enantiomeric or diastereomeric form, and any physiologically salt derivative thereof, for use in treating a subject in need of cancer treatment.

47 The use according to claim 46 wherein the rings A and B of Formula XIX together represent an 8-substituted quinoline system.

48 The use according to claim 46 or claim 47 wherein Z of Formula XIX represents -OH.

49 The use according to any one of claims 46 to 48 wherein Z of Formula XIX represents $-NH_2$.

50 The composition according to any one of claims 46 to 49 wherein R of Formula XIX is selected from one of



51 The composition according to any one of claims 46 to 50 wherein X of Formula XIX is $-CH_2Cl$.

52 The composition according to any one of claims 46 to 51 wherein Formula XIX represents one of the following

1-(chloromethyl)-5-hydroxy-3-(5,6,7-trimethoxyindol-2-ylcarbonyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-({5-[2-(dimethylamino)ethoxy]-1*H*-indol-2-yl}carbonyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-3-((2*E*)-3-{4-[2-(dimethylamino)ethoxy]phenyl}-5-hydroxy-2-propenoyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-3-[(5-methoxy-1*H*-indol-2-yl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

1-(chloromethyl)-5-hydroxy-3-[(2*E*)-3-(4-methoxyphenyl)-2-propenoyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinoline,

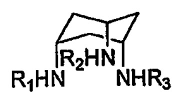
1-(chloromethyl)-3-[(2*E*)-3-(3-hydroxy-4-methoxyphenyl)-2-propenoyl]-2,3-dihydro-1*H*-pyrrolo[3,2-*f*]quinolin-5-ol, and

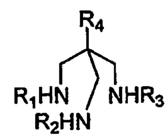
5-amino-1-(chloromethyl)-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-2,3-dihydro-*1H*-pyrrolo[3,2-*f*]quinoline.

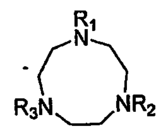
enantiomeric or diastereomeric forms, or any mixtures of such forms, and also any physiologically functional salt derivatives thereof.

53 A method of preparing a metal complex according to any one of claims 1 to 8 or 13 to 20, including the step of coupling a heterocyclic compound defined in any one of claims 25 to 31 with one or more of ligands L^1-L^4, wherein ligands L^1-L^4 are each independently selected in combinations from anionic monodentate ligands, including CN^-, SCN^-, halide, NO_3^-; bidentate ligands including MeCOCHJCOMe (Jacac; deprotonated in the complex), where J = H,

Me, Cl, SMe, SO_2Me, $S(CH_2)_nSO_3H$, $S(CH_2)_nCO_2H$, $S(CH_2)_nOP(O)(OH)_2$, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$, $S(CH_2)_nP(O)(OH)_2$ or $CH_2(CH_2)_nP(O)(OH)_2$, where each n is independently 1, 2, 3 or 4; or tridentate ligands **VIIIa-VIIIc** (=respectively TACH, TAME and TACN when R_1-R_3=H),

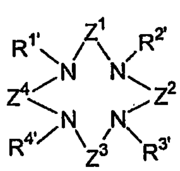

VIIIa


VIIIb


VIIIc

wherein R_1-R_4 are each independently selected from H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nOP(O)(OH)_2$ $CH_2(CH_2)_nP(O)(OH)_2$ or $CH_2(CH_2)_nNR^5{}_2$, where each n is independently 1, 2, 3 or 4 and each R^5 independently represents H, or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups or

L^1-L^4 can also be selected from any one of the tetradentate ligands **IX-XVII**, or any two of the bidentate ligands **XVIII**, or any combination of the bidentate ligands **XVIII** together with any of the monodentate ligands L^1-L^4 defined above;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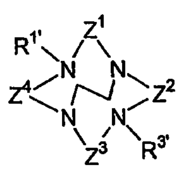
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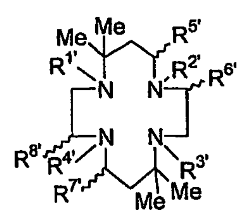
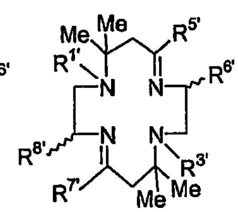

XI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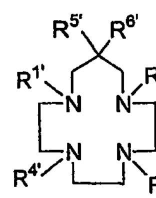
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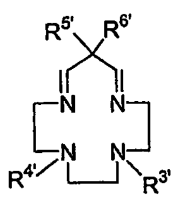
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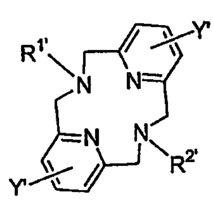
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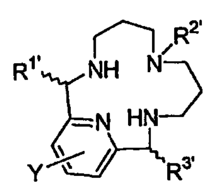
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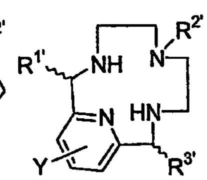
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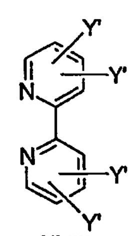
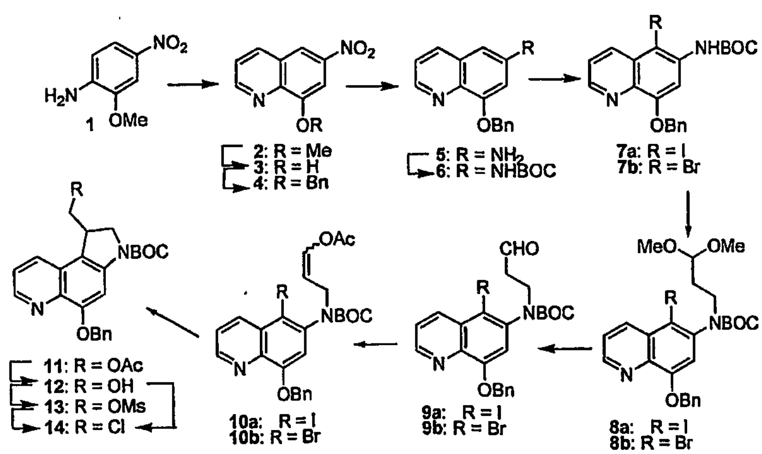

XVIII

wherein in formulae **IX-XVIII**, $R^{1'}$ to $R^{8'}$ each independently represent H, Me, $CH_2(CH_2)_nSO_3H$, $CH_2(CH_2)_nCO_2H$ or $CH_2(CH_2)_nOP(O)(OH)_2$ or $CH_2(CH_2)_nNMe_2$, where each n is independently 1, 2, 3 or 4;
each Z^1-Z^4 is independently selected from -$(CH_2)_2$-, -$(CH_2)_3$-, -CH_2OCH_2- or -$CH_2N(R^6)CH_2$-; where R^6 represents H, a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups and
each Y' is independently selected from H, halogen, SO_2Me, O(C_1-C_6alkyl), NR^7_2, where each R^7 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, or $Q^1(CH_2)_nQ^2$, wherein Q^1 is selected from –O-, -CH_2-, -NH-, -CONH-, -CO_2- or -SO_2-, and Q^2 is selected from -CO_2H, -SO_3H, -$OP(O)(OH)_2$ or –NR^8_2 where each R^8 is independently selected from H or a C_{1-6}alkyl optionally substituted with one or more hydroxy or amino groups, and wherein the ligands are complexed with a metal selected from Co^{III}, Co^{II}, Cr^{III} or Cr^{II}.

54 A method of preparing a heterocylic compound as defined in any one of claims 25 to 32, including the following reaction pathway



55 The method according to claim 54 including the further steps represented by the pathway

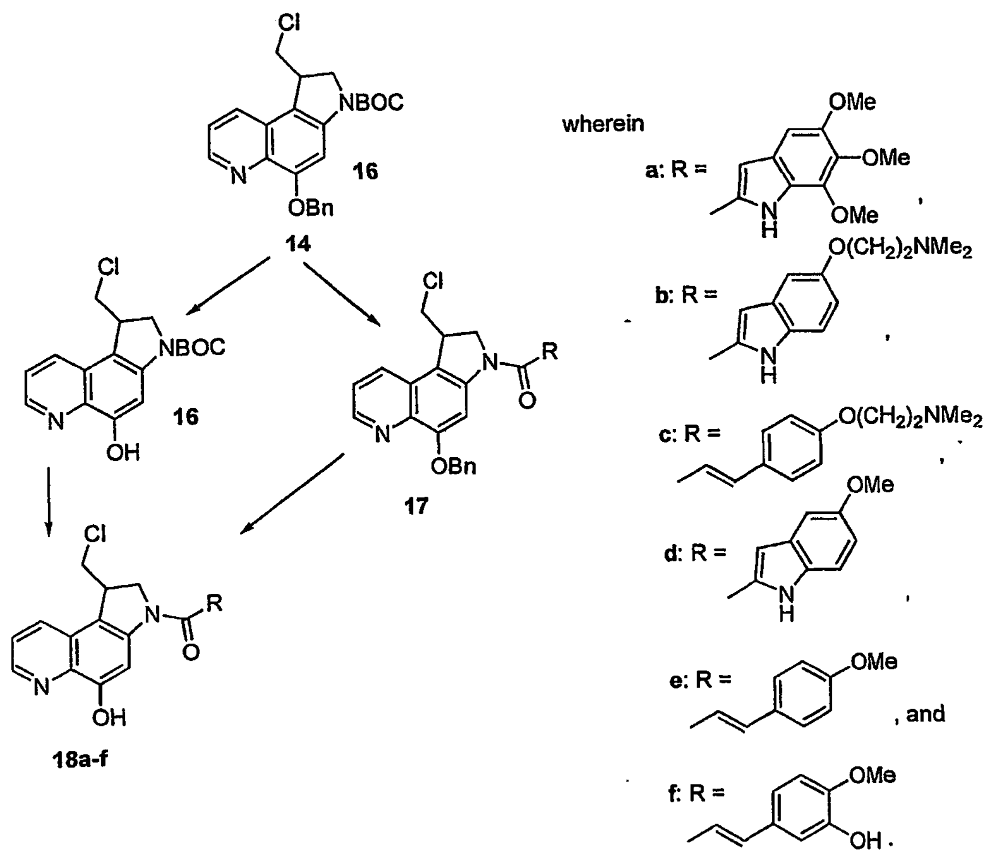

Cl
NBOC
16
OBn
14
NBOC
16
OH
R
O
OBn
17
18a-f
wherein
a: R =
OMe
OMe
OMe
b: R =
O(CH2)2NMe2
c: R =
O(CH2)2NMe2
d: R =
OMe
e: R =
OMe
, and
f: R =
OMe
OH.

Figure 1

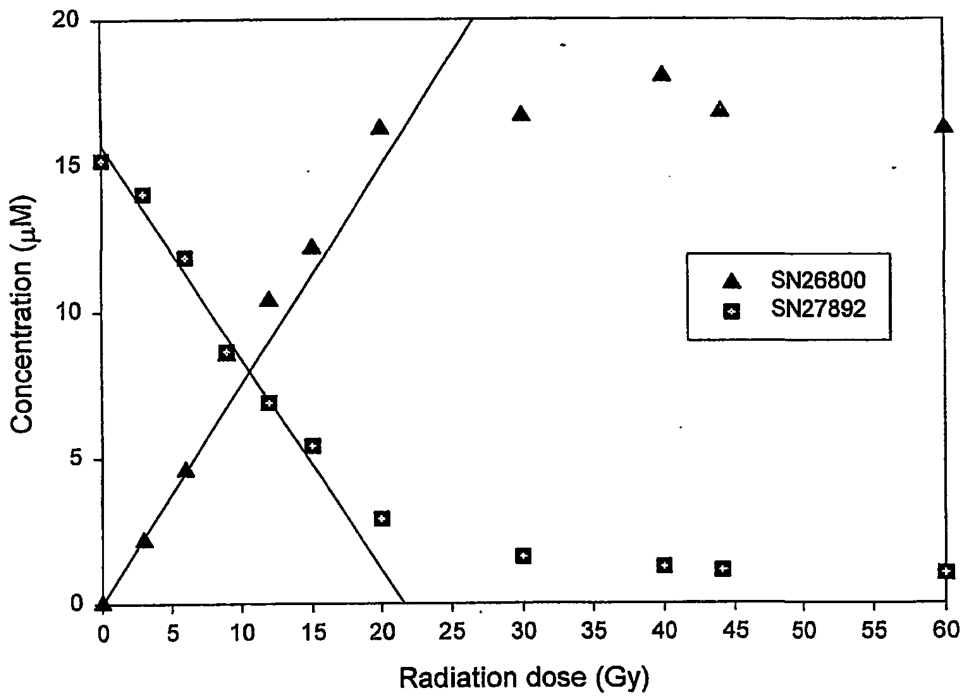
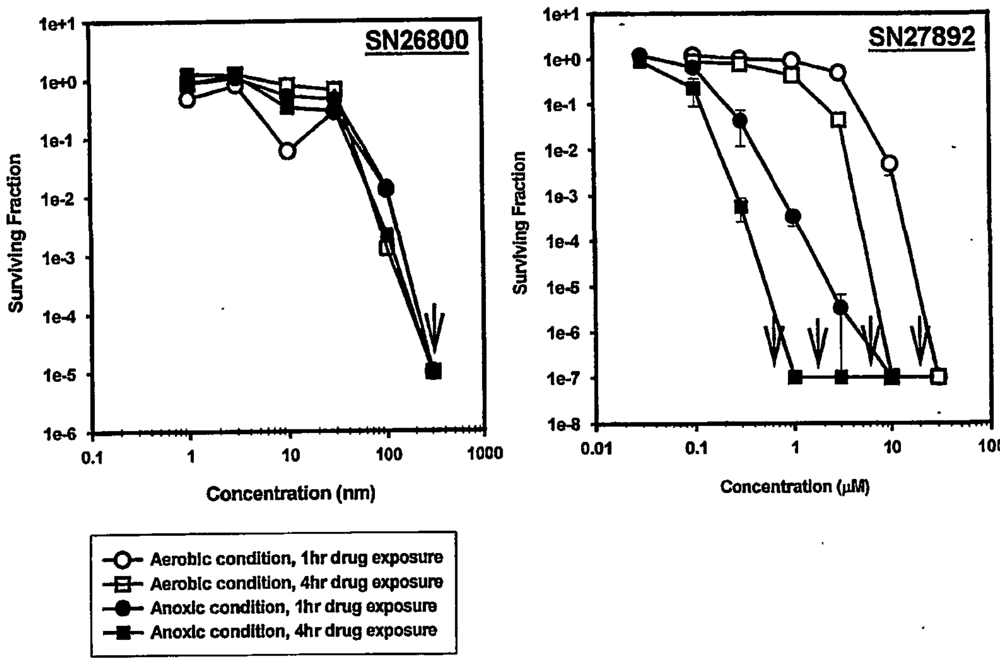

20
15
10
5
0
Concentration (μM)
0
5
10
15
20
25
30
35
40
45
50
55
60
Radiation dose (Gy)
SN26800
SN27892

Figure 2

Figure 2: Hypoxic Selectivity of complex M1 in HT29 cultures



The downwards arrows indicate no colonies recovered.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ02/00005

A.	**CLASSIFICATION OF SUBJECT MATTER**

Int. Cl. 7: C07D 471/04; C07F 15/06, 11/00; A61K 31/4745; A61P 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B.	**FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN sub-structure search of 1H-pyrrolo[3,2]quinoline in Chemical Abstracts

C.	**DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Organic Chemistry, Volume 65, No. 13, 2000, Boger, Dale L. and Boyce, Christopher W., "Selective Metal Cation Activation of a DNA Alkylating Agent: Synthesis and Evaluation of Methyl 1,2,9,9a-Tetrahydrocyclopropa[c]pyrido[3,2-e]indol-4-one-7-carboxylate (CPyI)", pages 4088 to 4100. **Reg. Nos. 280573-26-4, 280573-27-5, 280573-30-0, 280573-31-1, 280573-34-4, 280573-35-5, 280573-38-8, 280573-39-9, 280573-42-4, 280573-43-5, 280573-12-8, 280573-14-0, 280573-16-2, 280573-18-4, 280573-20-8.**	1-5, 13-17, 25-29, 32-36, 39-43, 46-50, 53
X	WO 01/83482 A (THE SCRIPPS RESEARCH INSTITUTE) 8 November 2001 See page 3 line 24, 25; page 4 line 13; page 20 line 7 and claim 22.	1-5, 13-17, 25-29, 32-36, 39-43, 46-50, 53

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 March 2002	- 8 APR 2002

Name and mailing address of the ISA/AU	Authorized officer
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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/NZ02/00005**

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
WO	01/83482	AU	62974/01	US	201543

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